MAY 26 1999

FREEDOM OF INFORMATION SUMMARY

NEW ANIMAL DRUG APPLICATION

NADA 141-152

REVOLUTION™
(selamectin)

"...kills adult fleas and prevents flea eggs from hatching for one month and is indicated for the prevention and control of flea infestations (*Ctenocephalides felis*), prevention of heartworm disease caused by *Dirofilaria immitis*, and the treatment and control of ear mite (*Otodectes cynotis*) infestations in cats and dogs. Revolution also is indicated for the treatment and control of sarcoptic mange (*Sarcoptes scabiei*) in dogs, and the treatment of intestinal hookworm (*Ancylostoma tubaeforme*) and roundworm (*Toxocara cati*) infections in cats. Revolution is recommended for use in dogs and cats six weeks of age and older."

Sponsored by:

PFIZER, INC

NADA 141-152

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TABLE OF CONTENTS

Page No.

I. GENERAL INFORMATION 1

II. INDICATIONS FOR USE 1

III. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND DOSAGE 1

IV. EFFECTIVENESS STUDIES FOR CATS 2

Dose Establishment 2
Effectiveness Confirmation - Fleas (Adults) 3
Effectiveness Confirmation - Fleas (Environmental Control/Prevention) 4
Effectiveness Confirmation - Prevention of Heartworm Disease 6
Effectiveness Confirmation - Ear Mites 8
Effectiveness Confirmation - Nematodes 10
Field Studies - Fleas 14
Field Studies - Ear Mites 16

V. ANIMAL SAFETY STUDIES FOR CATS 18

VI. EFFECTIVENESS STUDIES FOR DOGS 22

Dose Establishment 22
Effectiveness Confirmation - Fleas (Adults) 23
Effectiveness Confirmation - Fleas (Environmental Control/Prevention) 25
Effectiveness Confirmation - Prevention of Heartworm Disease 26
Effectiveness Confirmation - Ear Mites 28
Effectiveness Confirmation - Sarcoptic Mange 29
Field Studies - Fleas 30
Field Studies - Prevention of Heartworm Disease 32
Field Studies - Ear Mites 33
Field Studies - Sarcoptic Mange 35

VII. ANIMAL SAFETY STUDIES FOR DOGS 37

VIII. HUMAN SAFETY 43

IX. AGENCY CONCLUSIONS 44

X. LABELING (ATTACHED) 44

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

NADA Number: 141-152

Sponsor: Pfizer Inc.
235 East 42nd St.
New York, NY 10017

Generic Name: Selamectin

Trade Name: Revolution™

Marketing Status: Rx: U.S. Federal law restricts this drug to use by or on the order of a licensed veterinarian.

II. INDICATIONS FOR USE

Revolution kills adult fleas and prevents flea eggs from hatching for one month and is indicated for the prevention and control of flea infestations (*Ctenocephalides felis*), prevention of heartworm disease caused by *Dirofilaria immitis*, and the treatment and control of ear mite (*Otodectes cynotis*) infestations in dogs and cats. Revolution also is indicated for the treatment and control of sarcoptic mange (*Sarcoptes scabiei*) in dogs, and the treatment of intestinal hookworm (*Ancylostoma tubaeforme*) and roundworm (*Toxocara cati*) infections in cats. Revolution is recommended for use in dogs and cats six weeks of age and older.

III. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND DOSAGE

The recommended minimum dose is 2.7 mg selamectin per pound (6 mg/kg) of body weight. Administer the entire contents of a single dose tube of Revolution topically in accordance with the following tables.

Cats (lb)	Package color	mg per tube	Potency (mg/mL)	Administered volume (mL)
up to 5	Mauve	15 mg	60	0.25
5.1-15	Blue	45 mg	60	0.75

For cats over 15 lbs., use the appropriate combination of tubes

Dogs (lb)	Package color	mg per tube	Potency (mg/mL)	Administered volume (mL)
up to 5	Mauve	15 mg	60	0.25
5.1-10	Purple	30 mg	120	0.25
10.1-20	Brown	60 mg	120	0.5
20.1-40	Red	120 mg	120	1.0
40.1-85	Teal	240 mg	120	2.0

For dogs over 85 lbs., use the appropriate combination of tubes

IV. EFFECTIVENESS STUDIES FOR CATS

Dose Establishment

1. Flea Dose Determination Study: 1081E-60-95-154

Purpose: To compare the effectiveness 7, 14, 21, and 30 days after administration of 3 mg/kg, 6 mg/kg, and 9 mg/kg of selamectin as a single topical dose against *Ctenocephalides felis* on cats.

Investigator: M. S. Holbert

Study Location: Stillmeadow, Inc.
Sugar Land, Texas

Animals: 48 domestic shorthair cats (24 male, 24 female) 7 to 9 months of age, 12 cats per treatment group.

Dosage Groups: T1: Placebo (vehicle without active ingredient)
T2: Selamectin (3 mg/kg)
T3: Selamectin (6 mg/kg)
T4: Selamectin (9 mg/kg)

Route of Administration: Topical

Frequency of Treatment: Single treatment

Duration of Study: 30 days

Parameters Measured: Cats were infested with 100 unfed, viable adult fleas on days -3, 4, 11, 18, and 27. Flea comb counts were performed on days 0, 7, 14, 21, and 30.

Results: Percentage reduction in geometric mean flea counts for the three selamectin treatment groups (T2, T3, T4) ranged from 99.1% to 100% on days 7, 14, and 21. Effectiveness of selamectin against *Ctenocephalides felis* 30 days after treatment was 79.8%, 98.0% and 96.2% at 3, 6, and 9 mg/kg, respectively.

Conclusions: A dose of 6 mg/kg of selamectin was selected as a minimum dosage for effectiveness against fleas on cats 30 days after a single topical administration.

Adverse Drug Reactions: One cat in the 9 mg/kg group vomited 4 hours post-treatment which resolved without treatment. Another cat in the 9 mg/kg group was tachypneic at 2, 4, 8, and 24 hours post-treatment. The condition did not require treatment. One cat in the placebo group and two cats in the 3 mg/kg group developed localized irritation and swelling of the lips from 8 to 23 days post-treatment. The conditions resolved without treatment.

Effectiveness Confirmation - Fleas (Adults)

1. Effectiveness Confirmation Against Adult Fleas: 1081C-60-97-200

Purpose: To confirm effectiveness of selamectin at a single topical dose of 6 mg/kg against *Ctenocephalides felis* at 7, 14, 21, and 30 days in cats bathed 2 or 6 hours after treatment.

Investigator: M. S. Holbert

Study Location: Stillmeadow, Inc.
Sugar Land, Texas

Animals: 40 cats (20 males and 20 females) 5 to 6 months of age, 8 cats per treatment group.

Dosage Groups: T1: Placebo (vehicle without active ingredient), No bath
T2: Selamectin (≥6 mg/kg), no bath
T3: Selamectin (≥6 mg/kg), bathed 2 hrs after trtmt., water only
T4: Selamectin (≥6 mg/kg), bathed 2 hrs after trtmt., shampoo
T5: Selamectin (≥6 mg/kg), bathed 6 hrs after trtmt., shampoo

Route of Administration: Topical

Frequency of Treatment: Single treatment

Duration of Study: 30 days

Parameters Measured: Cats were infected with 100 unfed, viable adult fleas on days -7, 4, 11, 18, and 27. Flea comb counts were performed on days -4, 7, 14, 21, and 30.

Results: Effectiveness of 6 mg/kg selamectin against *C. felis* 7, 14 and 21 days after treatment ranged from 99.8% to 100%. On day 30, reductions were 99.3%, 99.4%, 97.1% and 98.0% for T2, T3, T4 and T5, respectively.

Conclusions: A single topical administration of selamectin which provided a minimum dosage of 6 mg/kg was effective against adult flea infestations for 30 days on cats, and bathing of cats with either water or non-insecticidal shampoo at 2 hours post-treatment or with shampoo at 6 hours post-treatment did not reduce the effectiveness of selamectin.

Adverse Drug Reactions: None observed

2. Effectiveness Confirmation Against Adult Fleas: 5081C-36-96-178

Purpose: To confirm the knockdown effectiveness of selamectin against fleas.

Investigator: Dr. M. G. Murphy

Study Location: Biological Laboratories Europe Ltd.
Mayo, Ireland

Animals: 44 cats (22 males and 22 females) 6 to 40 months of age, 4 cats per treatment group. .

Dosage Groups: T1: Non-medicated
T2-T6: Saline controls
T7: Selamectin (≥6mg/kg), flea count 12 hrs post-trtmt
T8: Selamectin (≥6mg/kg), flea count 24 hrs post-trtmt
T9: Selamectin (≥6mg/kg), flea count 36 hrs post-trtmt
T10: Selamectin (≥6mg/kg), flea count 42 hrs post-trtmt
T11: Selamectin (≥6mg/kg), flea count 48 hrs post-trtmt

Route of Administration: Topical

Frequency of Treatment: Single treatment

Duration of Study: 2 days

Parameters Measured: All cats were infested with 100 viable, unfed fleas on day –1. Comb counts of viable adult fleas present on T1 (non-medicated control) cats were performed 24 hours after infestation. The remaining cats were treated with saline or selamectin on day 0. Comb counts of viable adult fleas on cats in groups T7 – T11 and their corresponding saline-treated control groups (T2 – T6) were made at 12, 24, 36, 42, and 48 hours post-treatment, respectively.

Results: Percentage reductions in flea comb counts for selamectin at 12, 24, 36, 42 and 48 hours after treatment compared with the saline controls were 80.3%, 99.0%, 98.6%, 100%, and 100%, respectively.

Conclusions: A single topical administration of selamectin providing a minimum dosage of 6 mg/kg achieved a knockdown effectiveness of 90% between 12 and 24 hours after treatment.

Adverse Drug Reactions: One cat treated with selamectin (T9) had a residue and matted hair at the treatment site by 6 hours post-treatment. By 24 hours, the residue was gone but the matting persisted until the next observation time (36 hours).

Effectiveness Confirmation - Fleas (Environmental Control/Prevention)

1. Effectiveness Confirmation Against Pre-Adult Stages of Fleas: 1081C-60-95-186 and 1081C-60-97-198

Purpose: To confirm effectiveness of selamectin against pre-adult stages of fleas 30 days after treatment

Investigator: M. S. Holbert

Study Location: Stillmeadow, Inc
Sugar Land, Texas

Animals: 48 cats in both studies combined (25 males and 23 females) 5.4 to 32.0 months of age, 12 cats per treatment group.

Dosage Groups: T1: Placebo (vehicle without active ingredient)
T2: Selamectin (≥6 mg/kg)

Route of Administration: Topical

Frequency of Treatment: Single treatment

Duration of Study: 65 days

Parameters measured: On days 0, 4, 11, 18, and 27, each cat was infested with approximately 600 unfed viable adult fleas. Flea eggs were collected on days 3, 7, 14, 21, and 30 in each treatment group and incubated to determine viability. Larvae then were maintained under appropriate conditions to assess development to adult fleas.

Results: Treatment with selamectin reduced the number of eggs collected from treated animals in both studies by 99% compared to controls. Reductions of the proportions of flea eggs and larvae that developed to adult fleas following treatment with selamectin were 93.3% and 72.4%, respectively in study 1081C-60-97-198 and 100% for both flea eggs and larvae in study 1081C-60-95-186.

Conclusions: A single topical administration of selamectin providing a minimum dosage of 6 mg/kg was 99% effective in preventing the production of flea eggs for 30 days and in preventing the development of larval and adult fleas from eggs.

Adverse Drug Reactions: Two hours post-treatment, one cat treated with selamectin (1081C-60-97-198) had slight muscle tremors. The cat was normal at all other observations. On day 18, another cat treated with selamectin (1081C-60-97-198) had an area of alopecia with irritation approximately two inches caudal to the treatment site. By day 24, the irritation was gone (treated with Panalog®) but the alopecia persisted.

2. Effectiveness Confirmation For Prevention of Fleas: 5082C-36-97-180

Purpose: To confirm effectiveness of selamectin administered monthly for the prevention of flea infestations on cats.

Investigator: Dr. M. G. Murphy

Study Location: Biological Laboratories Europe, Ltd.
Mayo, Ireland

Animals: 40 cats (20 males and 20 females) 6 to 34 months of age, 20 cats per treatment group.

Dosage Groups: T1: Placebo (vehicle without active ingredient)
T2: Selamectin (≥6 mg/kg)

Route of Administration: Topical

Frequency of Treatment: Monthly for 2 months

Duration of Study: 60 days

Parameters measured: The cats were treated on days 0 and 30. Following treatment with selamectin cats were infested with 100 adult fleas and flea comb counts were performed on days 29, 44 and 60 to determine level of prevention.

Results: Mean flea comb counts performed on days 29, 44 and 60 showed that selamectin provided reductions of 100% on all count days compared with the placebo-treated cats.

Conclusions: Topical administration of selamectin providing a minimum dosage of 6 mg/kg was 100% effective in preventing the development of flea infestations on cats.

Adverse Drug Reactions: None observed

Effectiveness Confirmation - Prevention of Heartworm Disease

1. Effectiveness Confirmation In Prevention of Heartworm Disease: 1281E-60-95-155

Purpose: To confirm effectiveness of 6 mg/kg of selamectin against *Dirofilaria immitis* larvae inoculated 30, 45 or 60 days previously and of 3 mg/kg of selamectin against *D. immitis* larvae inoculated 30 or 45 days previously in cats.

Investigator: Dr. J. W. McCall

Study Location: T.R.S. Labs, Inc.
Athens, Georgia

Animals: 60 cats (30 males and 30 females) 5 to 7 months of age, 10 cats per treatment group.

Dosage Groups: T1: Placebo (vehicle without active ingredient)
T2: Selamectin (3 mg/kg), 30 days post-inoculation
T3: Selamectin (3 mg/kg), 45 days post-inoculation
T4: Selamectin (6 mg/kg), 30 days post-inoculation
T5: Selamectin (6 mg/kg), 45 days post-inoculation
T6: Selamectin (6 mg/kg), 60 days post-inoculation

Route of Administration: Topical

Frequency of Treatment: Single treatment

Duration of Study: 170 days

Parameters measured: Cats were necropsied 170 days after inoculation and the number of *D. immitis* worms were recorded.

Results: There was 100% prevention of heartworms in all groups of cats treated with selamectin. Six of the ten placebo treated cats had viable heartworms present at necropsy. The average number of heartworms found in the placebo group at necropsy was 3.1 with a range of 0 –9 worms.

Conclusions: Selamectin applied topically as a single dosage of 3 or 6 mg/kg was 100% effective in preventing the maturation of heartworms in cats following inoculation with infective *D. immitis* larvae 30 or 45 days prior to treatment, and 6 mg/kg was 100% effective in preventing maturation of heartworms following inoculation of infective larvae 60 days prior to treatment.

Adverse Drug Reactions: Approximately one-third of all animals in this study, including vehicle control, exhibited stiff hair or adherence of the hair at the treatment site.

2. Effectiveness Confirmation In Prevention of Heartworm Disease: 1281C-60-96-197

Purpose: To confirm effectiveness of 6 mg/kg of selamectin against *Dirofilaria immitis* larvae inoculated 30 days previously in cats, including cats bathed 24 hours after treatment.

Investigator: Dr. J. W. McCall

Study Location: T.R.S. Labs, Inc.
Athens, Georgia

Animals: 36 cats (18 males and 18 females) 4.6 to 5.3 months of age, 12 cats per treatment group.

Dosage Groups: T1: Placebo (vehicle without active ingredient)
T2: Selamectin (≥6 mg/kg)
T3: Selamectin (≥6 mg/kg), bathed 24 hrs after treatment

Route of Administration: Topical

Frequency of Treatment: Single treatment

Duration of Study: 169 days

Parameters measured: Cats were necropsied 169 days after inoculation and the number of *D. immitis* worms were recorded.

Results: There was 100% prevention of heartworms in both groups of cats treated with selamectin. Nine of the twelve placebo treated cats (75%) had viable

heartworms present at necropsy. The average number of worms found in the placebo group was 5.6 worms with a range of 0– 13 worms.

Conclusions: Selamectin applied topically as a single minimum dosage of 6 mg/kg was 100% effective in preventing the maturation of heartworms in cats inoculated with infective *D. immitis* larvae 30 days prior to treatment, including cats bathed 24 hours after treatment.

Adverse Drug Reactions: Fourteen of the 24 cats treated with selamectin (63%) had stiff/adhered hair at the treatment site from 2 – 24 hours after treatment. Eleven of 12 (92%) placebo-treated cats also showed stiff/adhered hair from 2 – 4 hours after treatment. One cat in the selamectin group that was bathed developed bilaterally symmetrical alopecia in the caudal lumbar region on day 46. Moderate regrowth was noticed by day 136.

Effectiveness Confirmation - Ear Mites

1. Effectiveness Confirmation Against *Otodectes cynotis* Ear Mites: 1082C-60-95-163

Purpose: To confirm effectiveness of selamectin at a single topical dose of 6 mg/kg against natural aural infestations of ear mites (*Otodectes cynotis*) in cats.

Investigator: D. D. Bowman

Study Location: CHK R & D, Inc.
Stanwood, Michigan

Animals: 20 cats (8 males, 12 females), ≥ 4 months of age, 10 cats per treatment group.

Dosage Groups: T1: Placebo (vehicle without active ingredient)
T2: Selamectin (≥6 mg/kg)

Route of Administration: Topical

Frequency of Treatment: Single treatment

Duration of Study: 30 days

Parameters Measured: Natural ear mite infestations were confirmed on Day –3. Quantitative ear mite counts were performed on day 30 by euthanizing the cats, removing the ear canals and examining the detritus for ear mites.

Results: Effectiveness of 6 mg/kg selamectin against *Otodectes cynotis* 30 days after treatment was 100%.

Conclusions: A single topical dose providing a minimum dosage of 6 mg/kg of selamectin was 100% effective against natural aural infestations of *Otodectes cynotis* mites in cats compared to the placebo.

Adverse Drug Reactions: One cat treated with selamectin vomited on day 1. One cat in the placebo group developed soft feces with blood and mucus on day 1.

2. Evaluation of the Effectiveness of Selamectin Against *Otodectes cynotis* in Cats: 5082E-60-94-153.

Purpose: To evaluate the effectiveness of 8 mg/kg selamectin administered topically against *Otodectes cynotis* in cats.

Investigator: Dr. D. D. Bowman

Study Locations: Cherry Hill, R&D
Stanwood, Michigan

Animals: 32 cats (19 females and 13 males) greater than 4 months of age, 8 per group. All cats were naturally infected with *O. cynotis*.

Dosage Groups:

Treatment	Dosage	Treatment Day	Males	Females
T1: Saline	0.1 ml/kg	Day 0	3	5
T2: Selamectin	≥8 mg/kg	Day 0	3	5
T3: Saline	0.1 ml/kg	Day 0 and 28	3	5
T4: Selamectin	≥8 mg/kg	Day 0 and 28	4	4

Route of Administration: Topical

Parameters measured: On day –7, cats were given a physical exam and the ears were examined for the presence of natural ear mite infections in both ear canals by otoscopic examination. Cats in groups T1 and T2 were euthanized on day 28 and cats in groups T3 and T4 were euthanized on day 56. At necropsy, the ear canals were dissected and live *O. cynotis* mites were counted.

Results: The geometric mean counts for mites in the treatment groups are outlined below:

	Geometric Mean Mite Counts	
Treatment Group	Day 28	Day 56
T1: Saline	143.5	NA
T2: Selamectin	0	NA
T3: Saline	NA	87
T4: Selamectin	NA	0

Percent reduction of the geometric mean mite counts from both T2 and T4 was 100%.

Conclusions: Topical administration of one or two doses of a minimum of 8 mg/kg selamectin was 100% effective against natural infestations of *Otodectes cynotis* in cats.

Adverse Drug Reactions: One cat in the T2 group developed alopecia and erythema with clear exudate between the shoulder blades on day 2. A scab had formed by day 4 and was resolved by day 8. A cat in the T4 group vomited on day 32, four days following the second treatment on day 28.

Effectiveness Confirmation - Nematodes

1. Effectiveness Confirmation Against Natural Infections of Adult Hookworms: 1282C-60-95-183

Purpose: To confirm effectiveness of a single dose of 6 mg/kg selamectin administered topically, against natural infections of adult hookworms (*Ancylostoma tubaeforme*) in cats.

Investigator: Dr. D. D. Bowman

Study Location: Cherry Hill Kennels R & D, Inc.
Stanwood, Michigan

Animals: 20 cats (5 males, 15 females), ≥4 months of age, 10 cats per treatment group.

Dosage Groups: T1: Placebo (vehicle without active ingredient)
T2: Selamectin (≥6 mg/kg)

Route of Administration: Topical

Frequency of Treatment: Single treatment

Duration of Study: 14 days

Parameters Measured: Hookworm counts were performed on worms isolated from the gastrointestinal tract after necropsy.

Results: Effectiveness of 6 mg/kg of selamectin against *Ancylostoma tubaeforme* in cats is shown in the following table:

Treatment	Geometric Mean *A. tubaeforme* Counts	% Reduction
T1: Placebo	24.4	N/A
T2: Selamectin	0.1	99.4%

Conclusions: A single topical dose providing a minimum dosage of 6 mg/kg of selamectin was 99% effective against natural infections of adult hookworms (*Ancylostoma tubaeforme*) in cats.

Adverse Drug Reactions: Three cats treated with selamectin developed soft stool on day 2. One cat treated with selamectin developed soft stool on day –2. Three other cats treated with the placebo (vehicle) also developed soft stool starting on day 0. One cat treated with the placebo developed soft stool with blood on day 2.

2. Effectiveness Confirmation Against Induced Infections of Adult Hookworms: 1281C-60-96-193

Purpose: To confirm effectiveness of one or two doses given at an interval of one month, of 6 mg/kg of selamectin, administered topically, against experimentally induced infections of adult hookworms (*Ancylostoma tubaeforme*) in cats.

Investigator: Dr. J. W. McCall

Study Location: TRS Labs, Inc.
Athens, Georgia

Animals: 32 cats (15 males, 17 females), ≥ 4 months of age, 8 cats per treatment group. The placebo group T1 had 4 females and 4 males and group T2 had 3 females and 4 males. The selamectin group T3 had 6 females and 2 males and group T4 had 4 females and 4 males.

Dosage Groups: T1: Placebo (vehicle without active ingredient)
T2: Placebo (vehicle without active ingredient)
T3: Selamectin (≥6 mg/kg)
T4: Selamectin (≥6 mg/kg)

Route of Administration: Topical

Frequency of Treatment: T1 and T3: Monthly x 1
T2 and T4: Monthly x 2

Duration of Study: 44 days

Parameters measured: Hookworm counts were performed on worms isolated from the gastrointestinal tracts after necropsy.

Results: Effectiveness of 6 mg/kg of selamectin against *A. tubaeforme* after one or two doses is shown in the following table:

Treatment	Geometric Mean *A. tubaeforme* Counts	% Reduction
T1: Placebo	93.5	N/A
T2: Placebo	75.2	N/A
T3: Selamectin	8.1	91.4%
T4: Selamectin	6.1	91.9%

Conclusions: Selamectin was 91% effective against adult hookworms (*Ancylostoma tubaeforme*) when administered at a minimum dosage of 6 mg/kg in either one or two topical doses given at monthly intervals.

Adverse Drug Reactions: On Day 0, eleven cats treated with the placebo (three in T1 and eight in T2) and nine cats treated with selamectin (four in T3 and five from T4) had stiff, clumped hair at the application site 2 to 4 hours after treatment. On Day 30, eight placebo (T2 group) cats and seven selamectin (T4 group) cats had stiff hairs at the application site after treatment.

3. Effectiveness Confirmation Against Natural Infections of Adult Ascarids: 1282C-60-95-184

Purpose: To confirm effectiveness of a single dose of 6 mg/kg of selamectin administered topically, against natural infections of adult ascarids (*Toxocara cati*) in cats.

Investigator: Dr. D. D. Bowman

Study Location: CHK R & D, Inc.
Stanwood, Michigan

Animals: 20 cats (8 males, 12 females), ≥4 months of age, 10 cats per treatment group.

Dosage Groups: T1: Placebo (vehicle without active ingredient)
T2: Selamectin (≥6 mg/kg)

Route of Administration: Topical

Frequency of Treatment: Single treatment

Duration of Study: 14 days

Parameters Measured: Ascarid worm counts were performed on worms isolated from the gastrointestinal tract after necropsy.

Results: Effectiveness of 6 mg/kg of selamectin against *T. cati* in cats is shown in the following table:

Treatment	Geometric Mean *T. cati* Counts	% Reduction
T1: Placebo	15.9	N/A
T2: Selamectin	0	100%

Conclusions: A single topical dose of a minimum dosage of 6 mg/kg of selamectin was 100% effective against natural infections of adult ascarids (*Toxocara cati)* in cats.

Adverse Drug Reactions: One cat treated with selamectin developed loose stool with blood on day 1 which resolved without treatment. One cat in the placebo group, developed diarrhea on day 0, which lasted until day 5.

4. Effectiveness Confirmation Against Induced Infections of Adult Roundworms and Hookworms: 1281C-60-95-162

Purpose: To confirm the effectiveness of a single unit dose of 6 mg/kg of selamectin administered topically, against experimentally induced infections of adult roundworms (*Toxocara cati*) and hookworms (*Ancylostoma tubaeforme*) in cats.

Investigator: Dr. J.W. McCall

Study Location: TRS Labs, Inc.
Athens, Georgia

Animals: 16 cats (9 males, 7 females), approximately 16 weeks of age, 8 cats per treatment group.

Dosage Groups: T1: Placebo (vehicle without active ingredient)
T2: Selamectin (≥6 mg/kg)

Route of Administration: Topical

Frequency of Treatment: Single treatment

Duration of Study: 14 days

Parameters Measured: *T. cati* and *A. tubaeforme* worm counts were performed on worms isolated from the gastrointestinal tract after necropsy.

Results: Effectiveness of 6 mg/kg of selamectin against *A. tubaeforme* and *T. cati* in cats is shown in the following table:

Treatment	Geometric Mean Worm Counts (% Reduction) *T. cati*	*A. tubaeforme*
T1: Placebo	20.3	40.7
T2: Selamectin	0 (100%)	6.2 (84.7%)

Conclusions: A single topical dose providing a minimum dosage of 6 mg/kg of selamectin was 100% effective against infections of adult roundworms (*Toxocara cati)* and was 84% effective against adult hookworms (*Ancylostoma tubaeforme)* in cats.

Adverse Drug Reactions: On day 0, three cats treated with placebo and two cats treated with selamectin had stiff, clumped hair at the application site two hours after treatment. The hairs were normal in appearance 12 hours post-treatment.

Field Studies - Fleas

1. Confirmation of effectiveness against fleas and safety of selamectin in cats presented as veterinary patients

Purpose: To confirm the effectiveness and safety of selamectin in the control of natural infestations of fleas on cats presented as veterinary patients.

Investigators/Study Locations:

Dr. Brett A Berryhill
Staring Animal Hospital
Baton Rouge, LA

Dr. Terry Clekis
VCA St. Petersburg Animal Hospital
St. Petersburg, FL

Dr. Mark W. Coleman
Suburban Animal Hospital
Gainesville, FL

Dr. H. Lee Butler
Huntingdon Animal Clinic
Huntingdon, TN

Dr. Stephen J. Ettinger
Range Avenue Veterinary Hospital
Los Angeles, CA

Dr. Tyrrel de Langley
Oakridge Animal Clinic
London, Ontario

Dr. Roger Sifferman
Bradford Park Veterinary Clinic
Springfield, MO

Dr. Yves Gosselin
Hospital Veterinaire Rive-Sud
Brossard, Quebec

Dr. Patricia Burke
Warwick Animal Hospital
Warwick, RI

Dr. Dennis A. Jackson
Granville Island Veterinary Hospital
Vancouver, British Columbia

Dr. David K. Lukof
Harleysville Veterinary Hospital
Harleysville, PA

Animals: A total of 304 client owned cats (158 males and 146 females) ranging in age from 6 weeks to 19 years were treated with selamectin in the clinical field study. A total of 189 of these cats were considered primary cases and included in the final effectiveness analysis. A total of 100 cats were treated with the positive control (pyrethrins with piperonyl butoxide) but only 66 cases were considered

primary and included in the effectiveness analysis. All treated cats were included in the evaluation of safety.

Dosage Groups: T1: Selamectin (≥6 mg/kg)
T2: Pyrethrins with piperonyl butoxide

Route of Administration: Topical application for both treatment groups

Frequency of Treatment: T1: Monthly for 3 months
T2: Weekly as needed for 3 months

Duration of Study: 90 days

Parameters Measured: Flea comb counts were performed on days 0, 14, 30, 60 and 90 following treatment. The clinical signs associated with fleas and flea allergy dermatitis (FAD) were assessed over the course of the study.

Results: Selamectin was 90% effective in controlling fleas after one dose and 98% effectiveness was maintained after the second and third doses.

Summary of Mean Flea Comb Counts and Percentage Reduction

Geometric Mean Flea Comb Counts

	Day 0	Day 14	Day 30	Day 60	Day 90
Selamectin	20.4	2.0	1.5	0.4	0.1
% Reduction	N/A	90.3%	92.5%	98.3%	99.3%
# Cats	189	186	179	174	167
Pyrethrins	17.7	7.8	6.0	4.6	3.3
% Reduction	N/A	55.9%	66.4%	73.9%	81.3%
# Cats	66	64	60	57	52

Cats treated with selamectin, including nine cats with pre-existing FAD, showed improvement in clinical signs associated with flea infestations (pruritus, erythema, scaling, papules, alopecia, dermatitis and pyodermatitis). This is considered a secondary effect of controlling fleas.

Conclusions: Selamectin administered topically at monthly intervals of the recommended minimum dosage of 6 mg/kg was safe and effective against natural infestations of fleas on cats presented as veterinary patients. A secondary effect of controlling the flea infestation was improvement in the clinical signs of flea infestations and FAD.

Adverse Drug Reactions: A total of 6 cats were observed to experience thinning of the haircoat with or without inflammation of the skin following treatment with selamectin.

One cat was withdrawn from the study due to persistent vomiting post-treatment. This same cat was also reported to be lethargic. One additional cat was reported to be lethargic following treatment and one cat was reported to be anorexic.

A human adverse reaction was reported: the owner of a cat treated with selamectin reported irritated eyes the evening after the third treatment. No further irritation was noted.

Field Studies - Ear Mites

1. Confirmation of effectiveness against ear mites and safety of selamectin in cats presented as veterinary patients

Purpose: To evaluate the effectiveness and safety of selamectin at a dosage of 6 mg/kg, administered topically as a single unit dose, in the treatment and control of natural infestations of ear mites (*Otodectes cynotis*) in cats presented as veterinary patients.

Investigators/Study Locations:

Dr. R. Hirsch
Range Avenue Veterinary Hospital
Denham Springs, LA

Dr. K. Harkewicz
Broadway Pet Hospital
Oakland, CA

Dr. H. Schutzman
Antioch Veterinary Hospital and Clinic
Antioch, CA

Dr. J. Murphy
Animal & Bird Medical Center
Palm Harbor, FL

Animals: A total of 68 client owned cats (37 males and 31 females) ranging in age from 6 weeks to 13 years were treated with selamectin in the field study and evaluated for safety. A total of 60 selamectin-treated cats were evaluated for the presence of ear mites on day 30 and included in the final analysis for effectiveness. A total of 35 client-owned cats were treated with the positive control (pyrethrins with piperonyl butoxide).

Dosage Groups: T1: Selamectin (≥6 mg/kg)
T2: Otomite (Pyrethrins with piperonyl butoxide)

Route of Administration: T1: Topical
T2: Ear canal (otic)

Frequency of Treatment: T1: Single treatment
T2: Once daily x 10 (repeated if necessary)

Duration of Study: 30 days

Parameters Measured: Effectiveness was assessed on the basis of a reduction in the severity of clinical signs of ear mites and the observation of viable ear mites directly or

otoscopically in the ears by microscopic examination of the debris collected at the three time points (day 0 and approximately days 14 and 30).

Results:
Summary of Effectiveness of Selamectin at 6 mg/kg in the Treatment and Control of Natural Infestations of *O. cynotis* in Cats Presented as Veterinary Patients: Percentage of Cats Without Viable *O. cynotis*.

	Cats Without Viable *O. cynotis*		
Treatment	**Day 0**	**Day 14**	**Day 30**
Selamectin			
Number of Cats free of mites/total	0/68	59/62	60/60
Percentage	0%	95.2%	100%
Otomite			
Number of Cats free of mites/total	0/35	31/33	26/28
Percentage	0%	93.9%	92.9%

Percent Differences and 95% Confidence Intervals of the Percentages of Cats without viable *O. cynotis* on Days 14 and 30.

Day	% Difference T1 – T2	Lower 95% CI	Upper 95% CI
14	1.2%	-8.5%	11.0%
30	7.1%	-2.4%	16.7%

Selamectin was shown to be no worse than the positive control for treating *O. cynotis* infestations.

Conclusions: Selamectin administered topically at a single dose at the recommended minimum dosage of 6 mg/kg was safe and effective against natural infestations of ear mites in cats presented as veterinary patients.

Adverse Drug Reactions: One cat treated with selamectin vomited beginning on day 0 and continued to vomit for 8 days. The cat was treated 8 days post-treatment with an antibiotic, antiemetic and an anthelmintic and was normal the following day.

V. ANIMAL SAFETY STUDIES FOR CATS

Five target animal safety studies were conducted in cats and kittens to address the tolerance and safety of selamectin.

1. Safety Margin/Toleration Study in Cats: 1482N-60-96-189

   Purpose: To evaluate the safety of selamectin at one, three, five and ten times the recommended unit dosage in kittens beginning at 6 weeks of age.
   Investigator: Dr. C. Steven Godin

   Study Location: White Eagle Toxicology Laboratories
   Doylestown, Pennsylvania

   Animals: 40 domestic shorthair kittens (20 male, 20 female), 6 weeks of age, 8 kittens per treatment group

   Dosage Groups: T1: Saline
   T2: Selamectin (≥6 mg/kg), 1x recommended dose
   T3: Selamectin (≥18 mg/kg), 3x recommended dose
   T4: Selamectin (≥30 mg/kg), 5x recommended dose
   T5: Selamectin (≥60 mg/kg), 10x recommended dose

   Route of Administration: Topical

   Frequency of Treatment: Once every 28 days for 7 treatments

   Duration of Study: 196 days

   Parameters Measured: Clinical observations were made before and at multiple times after treatment. General health of each cat was evaluated twice daily throughout the study. Blood, urine, and feces were collected and evaluated prior to each treatment on days –7, 28, 56, 84, 112, 140, 168, and at the end of the study for clinical pathology. Animals were necropsied at the end of the study and histopathology performed on selected organs. Immunohistochemistry was performed on brain specimens from saline-treated and 10x selamectin-treated animals.

   Results: Clumping of hair and a white residue at the treatment site were observed in all of the treatment groups. There were no clinically significant changes in clinical pathology variables during the study. No treatment related histopathological changes were detected.

   Conclusions: Topical administration of selamectin once every 28 days of one, three, five, and ten times the recommended minimum dosage of 6 mg/kg for seven treatments starting at 6 weeks of age was safe in male and female kittens.

2. Oral Safety of Selamectin in Cats: 1482N-60-96-191

Purpose: To evaluate the safety of selamectin administered orally to cats.

Investigator: Dr. Elizabeth I. Evans

Study Location: Midwest Research Institute
Kansas City, Missouri

Animals: 12 domestic shorthair cats (6 male, 6 female), ≥6 months of age, 6 cats per treatment group.
Dosage Groups: T1: Saline
T2: Selamectin (≥6 mg/kg)

Route of Administration: Oral

Frequency of Treatment: Single treatment

Duration of Study: 30 days

Parameters Measured: Clinical observations were made before and at multiple times after treatment. General health of each cat was evaluated at least twice daily throughout the study. Blood, urine, and feces were collected and evaluated prior to and at the end of the study for clinical pathology.

Results: There were no deaths in the study. Abnormal clinical observations were recorded in 4 of the 6 cats treated with selamectin. These observations consisted of salivation in 3 cats within 4 hours after treatment and intermittent vomiting in 2 cats during the 24 hours following dosing. Vomiting was also observed in these 2 cats on day 2 following treatment. There were no treatment related changes in clinical pathology.

Conclusions: Oral administration of a unit dose of selamectin at the recommended topical dose caused intermittent vomiting and salivation.

3. Safety Study in Heartworm Positive Cats: 5480N-60-94-151

Purpose: To evaluate the safety of 24 mg/kg selamectin administered topically once a month for six months in cats artificially infected with adult *Dirofilaria immitis*.

Investigator: Dr. John W. McCall

Study Location: TRS Labs, Inc.
Athens, Georgia

Animals: 46 domestic shorthair cats (22 male, 24 female) 8.9 to 9.9 months of age, 23 cats per treatment group

Dosage Groups: T1: Saline
T2: Selamectin (24 mg/kg), 4x recommended dose

Route of Administration: Topical

Frequency of Treatment: Once every 28 days for 6 treatments

Duration of Study: 196 days

Parameters Measured: Clinical observations were made before and at multiple times after treatment. General health of each cat was evaluated at least twice daily throughout the study. Blood was collected from each cat prior to each treatment on days 0, 28, 56, 84, 112, and 140, and also on days 1, 3, 7, 14, and 196, to examine for the presence of microfilariae. At the end of the study each cat was necropsied and the pleural cavity, precava, right atrium, right ventricle, and pulmonary arteries examined for heartworms.

Results: There were no deaths and no treatment-related adverse experiences in any of the heartworm-infected cats in the study.

Conclusions: Topical administration of selamectin once every 28 days for six treatments at four times the recommended minimum dosage of 6 mg/kg was safe in cats infected with viable adult *D. immitis*.

4. Reproductive Safety Study in Male Cats: 1486N-60-96-188

Purpose: To evaluate the safety of selamectin in breeding male cats.

Investigator: Dr. C. Steven Godin

Study Location: White Eagle Toxicology Laboratories
Doylestown, Pennsylvania

Animals: 20 adult male domestic shorthair cats, 10 cats per treatment group.

Dosage Groups: T1: Saline
T2: Selamectin (≥18 mg/kg), 3x recommended dose

Route of Administration: Topical

Frequency of Treatment: Once every 14 days for 16 to 17 treatments

Duration of Study: Approximately 10 months

Parameters Measured: Clinical observations were made before and at multiple times after treatment. General health of each cat was evaluated twice daily throughout the study. Blood, urine, and feces were collected and evaluated for clinical pathology approximately every 28 days and at the end of the study. Each male cat

was mated to 2 female cats. Within 24 hours of parturition of each female, all kittens were evaluated to determine litter size and the presence of congenital abnormalities. Any stillborn kittens were necropsied to determine cause of death. Conception rate [(number of females conceived/number of females exposed to mating) X 100] and queening index (total number of live kittens/number of pregnant females per treatment) were calculated.

Results: There were no adverse effects attributable to administration of selamectin in any of the clinical pathology variables or in any of the reproductive parameters measured in the study. There were a total of six stillborn kittens; 2 by placebo treated males and 4 by selamectin treated males. All stillborn kittens were normal upon necropsy. These deaths were not considered treatment related. Conception rates in females associated with both treatments were 100%. Queening indices were 4.2 and 3.9 for females mated to saline treated males and selamectin treated males, respectively.

Conclusions: Topical administration of selamectin once every 14 days for 16 to 17 treatments at three times the recommended minimum dosage of 6 mg/kg had no effect on the health or reproductive status of breeding male cats.

Adverse Drug Reactions: Clumping of hair at the treatment site with or without a white residue was observed up to 24 hours post-treatment in the selamectin treated group.

5. Reproductive Safety Study in Female Cats: 1486N-60-96-187

Purpose: To evaluate the safety of selamectin in breeding female cats.

Investigator: Dr. C. Steven Godin

Study Location: White Eagle Toxicology Laboratories
Doylestown, Pennsylvania

Animals: 44 adult female domestic shorthair cats, 11 cats per treatment group

Dosage Groups: T1: Saline, treatment initiated day 1 post-mating
T2: Saline, treatment initiated day 15 post-mating
T3: Selamectin (≥18 mg/kg), 3x, treatment initiated day 1 post-mating
T4: Selamectin (≥18 mg/kg), 3x, treatment initiated day 15 post-mating

Route of Administration: Topical

Frequency of Treatment: Once every 28 days

Duration of Study: 203 to 224 days

Parameters Measured: Clinical observations were made before and at multiple times after treatment. General health of each cat was evaluated twice daily throughout the study. Blood, urine, and feces were collected and evaluated for clinical pathology approximately every 28 days and at the end of the study. Females were mated and conception rate, queening index, and weaning index were calculated for each litter. All kittens were evaluated for the presence of congenital abnormalities. General health of each kitten was evaluated twice daily until weaning.

Results: There were no adverse effects attributable to administration of selamectin in any of the clinical pathology variables or in any of the reproductive parameters measured in the study.

Conclusions: Topical administration of selamectin once every 28 days at three times the recommended minimum dosage of 6 mg/kg had no effect on the health or reproductive status of breeding female cats.

Adverse Drug Reactions: Hair clumping, white residue, and hair discoloration were observed at the treatment site for all groups receiving selamectin treatment.

VI. EFFECTIVENESS STUDIES FOR DOGS

Dose Establishment

1. Flea Dose Determination Study: 1061E-60-95-163

Purpose: To compare the effectiveness 7, 14, 21, and 30 days after administration of 3 mg/kg, 6 mg/kg, and 9 mg/kg of selamectin as a single topical dose against *Ctenocephalides felis* on dogs.

Investigator: M. S. Holbert

Study Location: Stillmeadow, Inc.
Sugar Land, Texas

Animals: 48 beagle dogs (24 male, 24 female) 12 to 14 months of age, 12 dogs per treatment group.

Dosage Groups: T1: Placebo (vehicle without active ingredient)
T2: Selamectin (3 mg/kg)
T3: Selamectin (6 mg/kg)
T4: Selamectin (9 mg/kg)

Route of Administration: Topical

Frequency of Treatment: Single treatment

Duration of Study: 30 days

Parameters Measured: On day 0 dogs were treated topically with selamectin or placebo. On days 4, 11, 18, and 27, each dog was infested with approximately 100 unfed viable adult fleas. Flea comb counts of the number of viable fleas were performed on days 7, 14, 21, and 30.

Results: Percentage reduction in geometric mean flea counts for the three selamectin treatment groups ranged from 94.6% to 100% on days 7, 14, and 21. Effectiveness of selamectin against *Ctenocephalides felis* 30 days after treatment was 81.5%, 94.5% and 90.8% at 3, 6, and 9 mg/kg, respectively.

Conclusions: A dose of 6 mg/kg of selamectin was selected as a minimum dose for effectiveness against fleas on dogs 30 days following a single topical administration.

Adverse Drug Reactions: None observed

Effectiveness Confirmation - Fleas (Adults)

1. Effectiveness Confirmation Against Adult Fleas: 1061C-60-97-227

Purpose: To confirm the effectiveness of selamectin at a single topical dose of 6 mg/kg against fleas (*C. felis*) at 7, 14, 21, and 30 days in dogs bathed either 2 or 6 hours after treatment.

Investigator: M. S. Holbert

Study Location: Stillmeadow, Inc.
Sugar Land, Texas

Animals: 40 dogs (20 males and 20 females) 4.8 to 62 months of age, 8 dogs per treatment group.

Dosage Groups: T1: Placebo (vehicle without active ingredient), No bath
T2: Selamectin (≥6 mg/kg), No bath
T3: Selamectin (≥6 mg/kg), bathed 2 hrs. after trtmt., water only
T4: Selamectin (≥6 mg/kg), bathed 2 hrs. after trtmt., shampoo
T5: Selamectin (≥6 mg/kg), bathed 6 hrs. after trtmt., shampoo

Route of Administration: Topical

Frequency of Treatment: Single treatment

Duration of Study: 30 days

Parameters Measured: On day 0 dogs were treated topically with selamectin or placebo. On days 4, 11, 18, and 27, each dog was infested with approximately 100 unfed viable adult fleas. Flea comb counts of the number of viable fleas were performed on days 7, 14, 21, and 30.

Results: Reduction in geometric mean flea comb counts for the four selamectin treatments (T2, T3, T4, and T5) on days 7, 14 and 21 ranged from 99.8% to 100%. On day 30, percentage reductions were 100% for each treatment group (T2, T3, T4, and T5).

Conclusions: A single topical administration of selamectin which provided a minimum dosage of 6 mg/kg was effective against adult flea infestations for 30 days on dogs. Bathing of dogs with either water or non-insecticidal shampoo 2 hours after treatment or with shampoo 6 hours after treatment did not decrease the effectiveness of selamectin.

Adverse Drug Reactions: None observed

2. Effectiveness Confirmation Against Adult Fleas: 5061C-36-96-176

Purpose: To confirm the knockdown effectiveness of selamectin against fleas on dogs.

Investigator: Dr. M. G. Murphy

Study Location: Biological Laboratories Europe Ltd.
Mayo, Ireland

Animals: 44 dogs (22 males and 22 females) 6 to 41 months of age, 4 dogs per treatment group.

Dosage Groups: T1: Non-medicated
T2 - T6: Saline controls
T7: Selamectin (≥6 mg/kg), flea count 12 hrs. post-trtmt
T8: Selamectin (≥6 mg/kg), flea count 24 hrs. post-trtmt
T9: Selamectin (≥6 mg/kg), flea count 36 hrs. post-trtmt
T10: Selamectin (≥6 mg/kg), flea count 42 hrs. post-trtmt
T11: Selamectin (≥6 mg/kg), flea count 48 hrs. post-trtmt

Route of Administration: Topical

Frequency of Treatment: Single treatment

Duration of Study: 3 days

Results: Percentage reductions in flea comb counts for selamectin at 12, 24, 36, 42 and 48 hours after treatment compared with the saline treatments were 23.2%, 83.7%, 99.8%, 100% and 100%, respectively.

Conclusions: A single topical administration of selamectin providing a minimum dosage of 6 mg/kg achieved a knockdown effectiveness of 90% between 24 and 36 hours after treatment.

Adverse Drug Reactions: None observed

Effectiveness Confirmation - Fleas (Environmental Control/Prevention)

1. Effectiveness Confirmation Against Pre-Adult Stages of Fleas: 1061C-60-95-194 and 1061C-60-96-216

Purpose: To confirm effectiveness of selamectin against pre-adult stages of fleas 30 days after treatment.

Investigator: M. S. Holbert

Study Location: Stillmeadow, Inc.
Sugar Land, Texas

Animals: 24 dogs per study (12 males and 12 females) 5 to 26 months of age, 12 dogs per treatment group.

Dosage Groups: T1: Placebo (vehicle without active ingredient)
T2: Selamectin (≥6 mg/kg)

Route of Administration: Topical

Frequency of Treatment: Single treatment

Duration of Study: 65 days

Parameters measured: Flea eggs were collected from dogs infested with adult fleas in each treatment group and incubated to determine viability. Larvae were then maintained under appropriate conditions to assess development to adult fleas.

Results: Treatment with selamectin reduced the number of eggs collected from treated animals in both studies by 98% compared to controls. The numbers of flea eggs and larvae which developed following treatment with selamectin were reduced by 92.8% and 91.4%, respectively, in study 1061C-60-95-194 and 100% for both flea eggs and larvae in study 1061C-60-96-216.

1061C-60-95-194

	Geometric Mean # Eggs Incubated	Geometric Mean # Adult Fleas
Placebo	582.5	148
Selamectin	2.7	0.1

1061C-60-96-216

	Geometric Mean # Eggs Incubated	Geometric Mean # Adult Fleas
Placebo	992.7	170.1
Selamectin	6.2	0.0

Conclusions: A single topical administration of selamectin at a minimum dosage of 6 mg/kg was effective in preventing the production of flea eggs for 30 days and in preventing the development of larval and adult fleas from eggs.

Adverse Drug Reactions: None observed

Effectiveness Confirmation - Prevention of Heartworm Disease

1. Effectiveness Confirmation in Prevention of Heartworm Disease: 1261C-60-97-228

Purpose: To confirm effectiveness of selamectin at a single topical dose of 6 mg/kg against *Dirofilaria immitis* in dogs bathed 2 or 6 hours after treatment.

Investigator: Dr. J. W. McCall

Study Location: T.R.S. Labs, Inc.
Athens, Georgia

Animals: 40 dogs (20 males and 20 females) 5.7 to 8.5 months of age, 8 dogs per treatment group.

Dosage Groups: T1: Placebo (vehicle without active ingredient), no bath
T2: Selamectin (≥6 mg/kg), no bath
T3: Selamectin (≥6 mg/kg), bathed 2hrs after trtmt., water only
T4: Selamectin (≥6 mg/kg), bathed 2hrs after trtmt., shampoo
T5: Selamectin (≥6 mg/kg), bathed 6hrs after trtmt., shampoo

Route of Administration: Topical

Frequency of Treatment: Single treatment

Duration of Study: 140 days

Parameters measured: Dogs were necropsied 140 days after inoculation (110 days post-treatment) and the number of *D. immitis* worms were recorded.

Results: There was 100% prevention of maturation of heartworms in dogs treated with selamectin and bathed with either water 2 hours after treatment or with a non-insecticidal shampoo at either 2 or 6 hours after treatment. All of the placebo treated dogs had viable heartworms present at necropsy.

Treatment	Avg. Heartworm Counts	Prevention Rate
T1 Placebo (no bath)	29.75	N/A
T2 Selamectin (no bath)	0	100%
T3 Selamectin (bath 2hrs,water)	0	100%
T4 Selamectin (bath,2hrs)	0	100%
T5 Selamectin (bath 6 hrs)	0	100%

Conclusions: Selamectin applied topically at a minimum dosage of 6 mg/kg was 100% effective in preventing the maturation of heartworms in dogs inoculated with infective *D. immitis* larvae 30 days prior to treatment, with no decrease in effectiveness due to bathing with either water 2 hours after treatment or with a non-insecticidal shampoo at either 2 or 6 hours after treatment.

Adverse Drug Reactions: None observed

2. Effectiveness Confirmation in Prevention of Heartworm Disease: 1261E-60-95-162

Purpose: To confirm effectiveness of 6 mg/kg of selamectin against *Dirofilaria immitis* larvae inoculated 30, 45 or 60 days previously and of 3 mg/kg of selamectin against *D. immitis* larvae inoculated 30 or 45 days previously in dogs.

Investigator: Dr. J. W. McCall

Study Location: T.R.S. Labs, Inc.
Athens, Georgia

Animals: 36 dogs (18 males and 18 females) 7.5 to 11.4 months of age, 6 per group

Dosage Groups:
T1: Placebo (vehicle without active ingredient)
T2: Selamectin 3 mg/kg (30 days post-inoculation)
T3: Selamectin 3 mg/kg (45 days post-inoculation)
T4: Selamectin 6 mg/kg (30 days post-inoculation)
T5: Selamectin 6 mg/kg (45 days post-inoculation)
T6: Selamectin 6 mg/kg (60 days post-inoculation)

Route of Administration: Topical

Frequency of Treatment: Single treatment

Duration of Study: 140 days

Parameters measured: Dogs were necropsied 140 days after inoculation and the number of *D. immitis* worms were recorded.

Results: There was 100% prevention of heartworms in all groups of dogs treated with selamectin. All placebo-treated dogs had viable adult heartworms at necropsy.

Conclusions: Selamectin applied topically as a single dose of 3 or 6 mg/kg was 100% effective in preventing the maturation of heartworms in dogs following inoculation with infective *D. immitis* larvae 30 or 45 days prior to treatment, and 6 mg/kg was 100% effective in preventing maturation of heartworms following inoculation of infective larvae 60 days prior to treatment.

Adverse Drug Reactions: On the day of treatment, the following observations were noted at the treatment site on two dogs treated with selamectin: one dog had hairs adhered together and another dog had a dry, white residue present.

Effectiveness Confirmation - Ear Mites

1. Effectiveness Confirmation Against Ear Mites (*Otodectes cynotis*): 1062C-60-96-207

Purpose: To confirm the effectiveness of either one or two doses given at an interval of one month, of 6 mg/kg of selamectin administered topically, against natural infestations of ear mites in dogs.

Investigator: Dr. J. A. Hair

Study Location: Nu-Era Research Farms
Stillwater, Oklahoma

Animals: 24 dogs (9 males and 15 females), 1.6 to 8.0 years of age, 6 dogs per treatment group.

Dosage Groups: T1: Placebo (vehicle without active ingredient)
T2: Placebo (vehicle without active ingredient)
T3: Selamectin (≥6 mg/kg)
T4: Selamectin (≥6 mg/kg)

Route of Administration: Topical

Frequency of Treatment: T1 and T3: Monthly x 1
T2 and T4: Monthly x 2

Duration of Study: 60 days

Parameters measured: Qualitative otoscopic examination for the presence of mites was performed on all dogs on day 14. Quantitative mite counts were performed on day 30 for T1 and T3 dogs and on day 60 for T2 and T4 dogs.

Results: Selamectin was 100% effective against *O. cynotis* on both days 30 and 60.

Treatment	Geometric Mean *O. cynotis* Counts
T1 Placebo	23.4 (day 30)
T2 Placebo	70.0 (day 60)
T3 Selamectin	0 (day 30)
T4 Selamectin	0 (day 60)

Conclusions: One or two topical doses given at monthly intervals of a minimum dosage of 6 mg/kg of selamectin was 100% effective against natural aural infestations of *Otodectes cynotis* in dogs.

Adverse Drug Reactions: Twelve dogs treated with selamectin had hair matting at the site of application.

Effectiveness Confirmation - Sarcoptic Mange

1. Effectiveness Confirmation Against Sarcoptic Mange: 1062C-60-95-172

Purpose: To confirm effectiveness of either one or two doses given at an interval of one month, of the recommended minimum dosage 6 mg/kg of selamectin, administered topically, against natural infestations of sarcoptic mange in dogs.

Investigator: M. S. Holbert

Study Location: Stillmeadow, Inc.
Sugar Land, Texas

Animals: 30 dogs (16 males and 14 females), 15 weeks to 6 years of age, 15 dogs per treatment group.

Dosage Groups: T1: Placebo (vehicle without active ingredient)
T2: Selamectin (≥6 mg/kg)

Route of Administration: Topical

Frequency of Treatment: Monthly x 2

Duration of Study: 60 days

Parameters Measured: Natural infestations with *S. scabiei* were determined by skin scrapings. On days 14, 29, 44, and 60, skin scrapings and live *S. scabiei* counts were performed. Clinical assessments of mite infestations were also conducted.

Results: The geometric mean mite counts from skin scrapings performed on days 14, 30, 44 and 60 showed that selamectin provided reductions of 100%, 93.5%, 100% and 100%, respectively.

The table below shows the geometric mean counts.

Treatment	Day -3	Day 14	Day 30	Day 44	Day 60
T1 Placebo	5.3	3.3	3.7	1.1	1.1
T2 Selamectin	4.5	0	0.2	0	0

Clinical signs: Clinical signs of *S. scabiei* infestation were also recorded to assess efficacy. These were: pruritus, erythema, scaling/crusting, papules, alopecia (from self-trauma) and dermatitis/pyodermatitis. Both groups experienced a decrease in clinical signs. A higher percentage of dogs in the selamectin treated group showed improvement in clinical signs.

Conclusions: Topical administration of selamectin at one or two doses at monthly intervals of a minimum dosage of 6 mg/kg was >93% effective against natural infestations of *Sarcoptes scabiei* in dogs.

Adverse Drug Reactions: Abnormal health observations made 24 hours following treatment on day 0 include: one dog treated with the vehicle had mucoid stool, one dog treated with selamectin had diarrhea, two dogs treated with vehicle and one dog treated with selamectin developed pruritus. One dog treated with selamectin was enrolled into the study in a debilitated state due to overwhelming effects secondary to *S. scabiei* infection. Two hours after treatment, the dog had a decreased appetite. It appeared weak at the 24 hour assessment. This dog was treated symptomatically for infection, dehydration and anorexia, but never improved. The dog was euthanized for humane reasons.

Field Studies - Fleas

1. Confirmation of effectiveness against fleas and safety of selamectin in dogs presented as veterinary patients

Purpose: To confirm the effectiveness and safety of selamectin in the control of natural infestations of fleas on dogs presented as veterinary patients.

Investigators/Study Locations:

Dr. Brett A Berryhill
Staring Animal Hospital
Baton Rouge, LA

Dr. Patricia Burke
Warwick Animal Hospital
Warwick, RI

Dr. Mark W. Coleman
Suburban Animal Hospital
Gainesville, FL

Dr. Dennis A. Jackson
Granville Island Veterinary Hospital
Vancouver, British Columbia

Dr. Stephen J. Ettinger
Range Avenue Veterinary Hospital
Los Angeles, CA

Dr. Tyrrel de Langley
Oakridge Animal Clinic
London, Ontario

Dr. Thomas A Greene
Greene Veterinary Clinic
Livonia, LA

Dr. Yves Gosselin
Hospital Veterinaire Rive-Sud
Brossard, Quebec

Animals: A total of 311 client-owned dogs (154 males and 157 females) ranging in age from 8 weeks to 16 years were treated with selamectin in the field study. Two hundred and twenty of these dogs were primary cases and included in the final effectiveness analysis. The remaining 81 dogs were dogs residing in the same household as the primary dog and included in the safety analysis. Of the total of 115 client-owned dogs treated with the positive control (fenthion), 81 dogs were included in the final effectiveness analysis.

Dosage Groups: T1: Selamectin (≥6 mg/kg)
T2: Fenthion (4 to 8 mg/kg)

Route of Administration: Topical

Frequency of Treatment: T1: Monthly for 3 months
T2: label directions

Duration of Study: 90 days

Parameters Measured: Flea comb counts were performed on days 0, 14, 30, 60 and 90 following treatment. The clinical signs associated with fleas and flea allergy dermatitis (FAD) were assessed over the course of the study.

Results:

Summary of Mean Flea Comb Counts and Percentage Reduction

	Geometric Mean Flea Comb Counts				
	Day 0	**Day 14**	**Day 30**	**Day 60**	**Day 90**
Selamectin	27.0	2.9	2.2	0.3	0.1
% Reduction	N/A	89.4	92.0	99.0	99.8
# Dogs	220	214	212	203	198
Fenthion	15.1	4.1	2.9	2.1	2.2
% Reduction	N/A	72.8	81.1	86.1	85.6
# Dogs	81	71	71	68	61

Selamectin was 92% effective within 30 days of the first dose. The percent effectiveness achieved with subsequent doses increased to ≥99% with the second and third doses.

Dogs treated with selamectin, including 68 dogs with pre-existing FAD, showed improvement in clinical signs associated with flea infestations (pruritus, erythema, scaling, papules, alopecia, dermatitis, and pyodermatitis). This is considered a secondary effect of controlling fleas.

Conclusions: Selamectin administered topically at monthly intervals at the recommended minimum dosage of 6 mg/kg was safe and effective against natural infestations of fleas on dogs presented as veterinary patients. A secondary effect of controlling the fleas was improvement in the clinical signs of flea infestations and FAD.

Adverse Drug Reactions: A dog vomited after the first treatment with selamectin followed by a brief period (≤ 24 hours) of anorexia. The incident was mild and did not require treatment, and did not reoccur after the second and third dose administrations. Other clinical observations seen in one dog each included diarrhea, anorexia, residue at the treatment site and alopecia near the treatment site.

Field Studies - Prevention of Heartworm Disease

1. Confirmation of the effectiveness and safety of selamectin in the prevention of heartworm disease in dogs presented as veterinary patients

Purpose: To confirm the effectiveness and safety of selamectin in the prevention of heartworm disease in dogs presented as veterinary patients.

Investigators/Study Locations:

Dr. Lynn Buzhardt
The Animal Center, Inc
Zachary, LA

Dr. David K. Lukof
Harleysville Veterinary Hospital
Harleysville, PA

Dr. Terry Clekis
VCA St. Petersburg Animal Hospital
St. Petersburg, FL

Dr. Roger L. Sifferman
Bradford Park Veterinary Hospital
Springfield, MO

Animals: A total of 298 client owned dogs (146 males and 152 females) ranging in age from 7 weeks to 14 years were treated with selamectin in the field study and included in the final effectiveness analysis.

Dosage Groups: T1: Selamectin (≥6 mg/kg)
T2: Ivermectin (≥6 µg/kg)

Route of Administration: T1: Topical
T2: Oral

Frequency of Treatment: Monthly for 6 months

Duration of Study: 300 days

Parameters Measured: Tests to detect the presence of *D. immitis* microfilariae and adult heartworm antigen were conducted on days 180 and 300 following initial treatment.

Results: All animals in both groups were negative for blood microfilariae and adult heartworm antigen on days 180 and 300.

Conclusions: Selamectin administered topically at monthly intervals at the recommended minimum dosage of 6 mg/kg of selamectin was safe and 100% effective in the prevention of heartworm disease in dogs.

Adverse Drug Reactions: Two dogs from the same household were noted by the owner to both have loose stool approximately 18 hours after each administration of selamectin. Other clinical observations seen in dogs treated with selamectin include: vomiting (in 3 dogs), diarrhea/loose stools (in 3 dogs), treatment site residue (in 1 dog), and salivation (in 1 dog).

Field Studies - Ear Mites

1. Confirmation of effectiveness against ear mites and safety of selamectin in dogs presented as veterinary patients

Purpose: To evaluate the effectiveness and safety of selamectin at a minimum dosage of 6 mg/kg administered topically twice at an interval of one month between each dose for the treatment and control of natural infestations of *Otodectes cynotis* in dogs presented as veterinary patients.

Investigators/Study Locations:

Dr. S. M. Hirsch
Range Avenue Veterinary Hospital
Denham Springs, LA

Dr. J. Murphy
Animal and Bird Medical Center
Palm Harbor, FL

Dr. H. Schutzman
Antioch Veterinary Hospital
Antioch, CA

Dr. L. F. Buzhardt
The Animal Center, Inc.
Zachary, LA

Dr. H. L. Butler
Huntingdon Animal Clinic
Huntingdon, TN

Dr. K. E. Acre, Sr.
Altamonte Veterinary Hospital
Altamonte Springs, FL

Dr. R. L. Sifferman
Bradford Park Veterinary Hospital
Springfield, MO

Animals: A total of 90 client owned dogs (39 males and 51 females) ranging in age from 6 weeks to 13 years were treated with selamectin in the field study; 83 dogs completed the study to day 60. Forty dogs were treated with the positive control and completed the study.

Dosage Groups: T1: Selamectin (≥6 mg/kg)
T2: Otomite (Pyrethrins/piperonyl butoxide)

Route of Administration: T1: Topical
T2: Ear canal (otic)

Frequency of Treatment: T1: Monthly x 2
T2: Once daily x 10

Duration of Study: 60 days

Parameters Measured: Effectiveness was assessed on the basis of a reduction in the severity of clinical signs of *O. cynotis* and the presence or absence of live *O. cynotis* in the ears. Mites were visualized directly by otoscopic examination or by microscopic examination of the debris collected at four time points (day 0, and approximately days 14, 30 and 60).

Results:

Summary of Effectiveness of Selamectin at 6 mg/kg in the Treatment and Control of Natural Infestations of *Otodectes cynotis* in Dogs Presented as Veterinary Patients: Number and Percentage of Dogs Without Viable *Otodectes cynotis* at each Assessment.

Treatment	Dogs Without Viable *O. cynotis* Day 0	Day 14	Day 30	Day 60
Selamectin				
Number of Dogs free of mites/total	0/90	47/88	65/84	75/83
Percentage	0%	53.4%	77.4%	90.4%
Otomite				
Number of Dogs free of mites/total	0/45	21/43	28/41	26/40
Percentage	0%	48.8%	68.3%	65.0%

Percent Differences and 95% Confidence Intervals of the Percentages of Dogs without viable *O. cynotis* on Days 14 and 30.

Day	% Difference (T1 - T2)	Lower 95% CI	Upper 95% CI
14	4.6%	-13.7%	22.8%
30	9.1%	-7.7%	25.9%
60	25.4%	9.3%	41.5%

Selamectin was shown to be no worse than the positive control for treating *O. cynotis* infestations.

Percentage of Dogs with Clinical Signs of *O. cynotis*

Clinical Sign	Treatment	Day 0	Day 14	Day 30	Day 60
Head shaking	Selamectin	72.2%	52.3%	48.8%	21.7%
	Otomite	75.5%	55.8%	51.2%	45.0%
Pruritus of Ears	Selamectin	72.2%	47.7%	21.4%	12.0%
	Otomite	73.3%	39.5%	24.3%	30.0%
Erythema of Ear canal	Selamectin	70.0%	46.6%	33.9%	18.1%
	Otomite	86.7%	58.1%	56.1%	38.8%
Pinnal trauma/ Alopecia	Selamectin	45.6%	31.8%	14.3%	6.6%
	Otomite	43.3%	34.9%	22.0%	16.3%
Ulceration of Canal	Selamectin	27.2%	18.2%	6.5%	4.2%
	Otomite	28.9%	16.3%	18.3%	11.3%
Debris in Canal	Selamectin	94.4%	90.3%	87.5%	71.1%
	Otomite	96.7%	93.0%	90.2%	83.8%

Conclusions: Selamectin is safe and effective for treatment and control of *O. cynotis* in the dog when used at the recommended minimum dosage of 6 mg/kg. In this clinical field trial, 90% effectiveness was achieved after the second treatment with selamectin. The ears were not cleaned during the study and at day 60, 71.1% of the dogs treated with selamectin still had visible debris in the ear canal.

Adverse Drug Reactions: None observed

Field Studies - Sarcoptic Mange

1. Confirmation of effectiveness against sarcoptic mange and safety of selamectin in dogs presented as veterinary patients

Purpose: To evaluate the effectiveness and safety of selamectin at the recommended minimum dosage of 6 mg/kg administered topically and evaluated after one dose or two doses applied at an interval of one month for the treatment and control of natural infestations of *Sarcoptes scabiei* in dogs presented as veterinary patients.

Investigators/Study Locations:

Dr. Harkewicz
Broadway Pet Hospital
Oakland, CA

Dr. Herrington
Hollywood Animal Hospital
Hollywood, FL

Dr. Greene
Greene Veterinary Clinic
Livonia, LA

Dr. Sifferman
Bradford Park Veterinary Hospital
Springfield, MO

Dr. Butler
Huntingdon Animal Clinic
Huntingdon, TN

Animals: A total of 75 client owned dogs (33 males and 42 females) ranging in age from 6 weeks to 16 years were treated with selamectin in the field study; 54 dogs completed the study to day 60. Twenty-three dogs were treated with the positive control. Fifteen of these dogs completed the study.

Dosage Groups: T1: Selamectin (≥6 mg/kg)
T2: Paramite® (N-(Mercaptomethyl) phthalimide S-(0,0-Dimethyl phosphorodithioate))

Route of Administration: Topical

Frequency of Treatment: T1: Monthly x 2
T2: Every 7 days, as needed

Duration of Study: 60 days

Parameters Measured: Effectiveness was assessed on the basis of a reduction in the severity of clinical signs of *S. scabiei* at several time points (days 0, 14, 30, and 60) compared to day 0. These included pruritus, erythema, scaling/crusting, papules, alopecia, and dermatitis/pyodermatitis. Detection of viable *Sarcoptes scabiei* microscopically from skin scrapings at several time points (days 0, 30 and 60) was also used to assess effectiveness.

Results:
Summary of Effectiveness of Selamectin at 6 mg/kg in the Treatment and Control of Natural Infestations of *S. scabiei* in Dogs Presented as Veterinary Patients: Number and Percentage of Dogs Without Viable *S. scabiei* (Larvae, Nymphs, or Adults) at each Assessment.

	Dogs Without Viable *S. scabiei*		
Treatment	**Day 0**	**Day 30**	**Day 60**
Selamectin			
Number of Dogs free of mites/total	0/75	59/62	54/54
Percentage	0%	95.2%	100%
Paramite®			
Number of Dogs free of mites/total	0/23	20/20	19/19
Percentage	0%	100.0%	100.0%

Percent Differences and 95% Confidence Intervals of the Percentages of Dogs without viable *S. scabiei* on Day 30.

Day	% Difference (T1 - T2)	Lower 95% CI	Upper 95% CI
30	-4.8%	-10.2%	0.5%

Selamectin was shown to be no worse than the positive control for treating *S. scabiei* infestations.

Percentage of Dogs with Clinical Signs of *S. scabiei*

Clinical Sign	Treatment	Day 0	Day 14	Day 30	Day 60
Pruritus	Selamectin	98.7%	85.5%	53.1%	10.7%
	Paramite®	95.7%	65.0%	33.3%	10.5%
Erythema	Selamectin	96.0%	66.7%	40.6%	1.8%
	Paramite®	100.0%	60.0%	19.0%	10.5%
Scaling/ Crusting	Selamectin	98.7%	88.4%	64.1%	16.1%
	Paramite®	95.7%	95.0%	66.7%	10.5%
Papules	Selamectin	86.7%	52.2%	29.7%	5.4%
	Paramite®	87.0%	45.0%	14.3%	0%

Clinical Sign	Treatment	Day 0	Day 14	Day 30	Day 60
Alopecia	Selamectin	93.3%	85.5%	73.4%	14.3%
	Paramite®	95.7%	90.0%	47.6%	5.3%
Dermatitis/ Pyodermatitis	Selamectin	88.0%	59.4%	31.3%	12.5%
	Paramite®	91.3%	45.0%	23.8%	5.3%

Conclusions: Selamectin administered topically and evaluated after either one or two doses at monthly intervals at the recommended minimum dosage of 6 mg/kg was safe and effective against natural infestations of *Sarcoptes scabiei* in dogs presented as veterinary patients.

Adverse Drug Reactions: One dog treated with selamectin was sedated with ketamine and diazepam on the first day of treatment. The owner reported that the dog had been very lethargic and anorexic for 5 days afterward. This same dog vomited several times in the 24 hour period following the second dose of selamectin. A dog died four days after being treated with the first dose of selamectin. The dog was debilitated when presented to the veterinary clinic. It was anemic and had hookworm ova on fecal analysis. The dog was treated with Strongid-T® for two days, force-fed and given a blood transfusion on day 3. The dog died on day 4.

VII. ANIMAL SAFETY STUDIES FOR DOGS

Six target animal safety studies were conducted in dogs and puppies to address the tolerance and safety of selamectin.

1. Safety Margin/Toleration Study in Dogs: 1462N-60-96-197

Purpose: To evaluate the safety of selamectin at one, three, five and ten times the recommended unit dosage in puppies beginning at 6 weeks of age.

Investigator: Dr. C. Steven Godin

Study Location: White Eagle Toxicology Laboratories
Doylestown, Pennsylvania

Animals: 40 beagle puppies (20 male, 20 female), 6 weeks of age, 8 dogs per treatment group.

Dosage Groups: T1: Saline
T2: Selamectin (≥6 mg/kg), 1x recommended dose
T3: Selamectin (≥18 mg/kg), 3x recommended dose
T4: Selamectin (≥30 mg/kg), 5x recommended dose
T5: Selamectin (≥60 mg/kg), 10x recommended dose

Route of Administration: Topical

Frequency of Treatment: Once every 28 days for 7 treatments

Duration of Study: 196 days

Parameters Measured: Clinical observations were made before and at multiple times immediately after treatment. General health of each dog was evaluated twice daily throughout the study. Blood, urine, and feces were collected and evaluated prior to each treatment and at the end of the study for clinical pathology. All animals were necropsied at the end of the study. Histopathology was performed on selected organs on all animals in the placebo and 10x groups. Immunohistochemistry for glial fibrillary acidic protein (a marker of nervous tissue injury) was performed on brain specimens from dogs in the saline-treated and the 10x selamectin-treated groups.

Results: There were no treatment-related effects in any of the dogs in the study. There were no clinically significant changes in clinical pathology variables during the study. No treatment related histopathological changes were detected in the study. Hair clumping, powdery residue, and hair discoloration were commonly observed at the treatment site in all groups receiving the test article.

Conclusions: Topical administration of selamectin once every 28 days at one, three, five, and ten times the recommended minimum dosage of 6 mg/kg for seven treatments starting at 6 weeks of age was safe in male and female puppies.

2. Oral Safety of Selamectin in Dogs: 1462N-60-96-200

Purpose: To evaluate the safety of selamectin administered orally to dogs.

Investigator: Dr. Elizabeth I. Evans

Study Location: Midwest Research Institute
Kansas City, Missouri

Animals: 12 beagle dogs (6 male, 6 female) 5 to 8 months of age, 6 dogs per treatment group.

Dosage Groups: T1: Saline
T2: Selamectin (≥6 mg/kg)

Route of Administration: Oral

Frequency of Treatment: Single treatment

Duration of Study: 30 days

Parameters Measured: Clinical observations were made before and at multiple times immediately after treatment. General health of each dog was evaluated at least twice daily throughout the study. Blood, urine, and feces were collected and evaluated prior to and at the end of the study for clinical pathology.

Results: There were no deaths and no treatment-related adverse effects in any of the dogs in the study.

Conclusions: Oral administration of a unit dose of selamectin at the recommended topical dose produced no adverse effects or signs of toxicity in either male or female beagle dogs.

3. Safety Study in Heartworm Positive Dogs: 1462N-60-96-199

Purpose: To evaluate the safety of selamectin in dogs infected with adult *Dirofilaria immitis*.

Investigator: Dr. John W. McCall

Study Location: TRS Labs, Inc.
Athens, Georgia

Animals: 20 beagle dogs (10 male, 10 female) 6.3 to 7.2 months of age, 10 dogs per treatment group. On day –28, all dogs were given adult heartworms by intravenous transplantation via the jugular vein.

Dosage Groups: T1: Saline
T2: Selamectin (≥18 mg/kg), 3x recommended dose

Route of Administration: Topical

Frequency of Treatment: Once every 28 days for 3 treatments

Duration of Study: 84 days

Parameters Measured: Clinical observations were made before and at multiple times immediately after treatment. General health of each dog was evaluated at least twice daily throughout the study. Blood, urine, and feces were collected and evaluated prior to each treatment and at the end of the study for clinical pathology and assessment of microfilariae and adult heartworm antigen. On days 0, 3, 7, and 14, blood was also collected and examined for microfilariae and adult heartworm antigen. At the end of the study each dog was necropsied and the pleural cavity, precava, right atrium, right ventricle, and pulmonary arteries examined for heartworms.

Results: Heartworm microfilariae were seen in all 20 dogs prior to treatment on day 0. For dogs treated with selamectin, microfilarial counts increased through day 7 and then gradually declined thereafter. All dogs tested heartworm antigen positive throughout the study. There were no deaths and no treatment-related adverse reactions in any of the heartworm-infected dogs in the study. Values for clinical pathologic parameters were not affected by treatment with selamectin. Stiff hair with a white residue was a consistent finding in groups receiving the test article.

Conclusions: Topical administration of selamectin once every 28 days for three treatments at three times the recommended minimum dosage of 6 mg/kg was safe in dogs infected with viable adult *D. immitis*.

4. Safety Study in Avermectin-Sensitive Collies: 1462N-60-96-198

Purpose: To evaluate the safety of selamectin in avermectin-sensitive Collie dogs.

Investigator: Dr. Elizabeth I. Evans

Study Location: Midwest Research Institute
Kansas City, Missouri

Animals: 24 avermectin-sensitive Collie dogs (15 male, 9 female), 6 dogs per treatment group.

Dosage Groups: T1: Placebo (vehicle without active ingredient)
T2: Selamectin (≥6 mg/kg), 1x recommended dose
T3: Selamectin (≥18 mg/kg), 3x recommended dose
T4: Selamectin (≥30 mg/kg), 5x recommended dose

Route of Administration: Topical

Frequency of Treatment: Once every 28 days for 3 treatments

Duration of Study: 84 days

Parameters Measured: Clinical observations were made before and at multiple times after treatment. General health of each dog was evaluated at multiple times daily throughout the study. Animals were observed for neurological signs typical of avermectin toxicosis (depression, ataxia, abnormal mydriasis, abnormal salivation, and abnormal muscle fasciculations). Blood, urine, and feces were collected and evaluated prior to each treatment and at the end of the study for clinical pathology.

Results: There were no deaths in any of the dogs in the study. Salivation was the only clinical observation noted during the study. It was observed in two dogs from the placebo group, four dogs from the 1x group, one dog from the 3x group, and three dogs from the 5x group. Two dogs vomited during the study. One was treated with placebo and vomited two days following the third treatment. The other dog was treated with 5x selamectin and vomited one day after the second treatment and again eight days following the second treatment. There were no clinically significant changes in clinical pathology variables during the study.

Conclusions: Topical administration of selamectin once every 28 days for three treatments at one, three, or five times the recommended minimum dosage of 6 mg/kg was safe in avermectin-sensitive Collie dogs. Salivation was seen sporadically in all treatment groups.

5. Safety of Selamectin After Oral Dosing (in Sesame Oil) to Avermectin Sensitive Collie Dogs

Purpose: To evaluate the oral safety of selamectin in avermectin-sensitive Collie dogs.

Investigator: Dr. Larry Cruthers

Study Location: PLRS
Corapeake, North Carolina

Animals: 4 avermectin-sensitive Collie dogs (2 male, 2 female)

Dosages Tested: The final market formulation was not used in this study. No control was used.

Selamectin, 2.5 mg/kg
Selamectin, 5.0 mg/kg
Selamectin, 10.0 mg/kg
Selamectin, 15.0 mg/kg

Route of Administration: Oral

Frequency of Treatment: All dogs received each dose of selamectin in this escalating dose study. The treatments were administered on Days 0, 7, 14 and 22.

Duration of Study: 28 days

Parameters Measured: Clinical observations for neurological signs typical of avermectin toxicosis (depression, ataxia, abnormal mydriasis, abnormal salivation and abnormal muscle fasciculations) were made before treatment and at 2, 4, 6, and 8 hours after treatment, three times daily on days 1, 2, 3 and 4 following each treatment and twice daily on days 5 and 6 following each treatment.

Results: There were no deaths in this study. No treatment related effects occurred following treatment with 2.5, 10, and 15 mg/kg. One dog showed slight signs of ataxia 8 hours after treatment with 5.0 mg/kg, continuing into the next day (Day 8 of the study). This sign resolved and no other reactions were noted in this dog, even after the subsequent treatments with 10 and 15 mg/kg.

Conclusions: Oral administration of selamectin to avermectin-sensitive Collies at a point dose of 15 mg/kg, (1.2-2.1X the minimum recommended topical dose), caused no adverse effects. However, mild ataxia was noted in one dog following oral treatment with 5 mg/kg (0.4 - 0.7X the minimum recommended topical dose).

6. Reproductive Safety Study in Male Dogs: 1466N-60-96-196

Purpose: To evaluate the safety of selamectin in breeding male dogs.

Investigator: Juliann Ehrhart

Study Location: White Eagle Toxicology Laboratories
Doylestown, Pennsylvania

Animals: Twenty mature male beagle dogs, 10 per treatment group. All dogs were documented sires of at least two recent litters of at least four puppies per litter with no congenital abnormalities in any puppies. Forty mature female beagles was used for breeding and did not receive any treatment.

Dosage Groups: T1: Saline
T2: Selamectin (≥18 mg/kg), 3x recommended dose

Route of Administration: Topical

Frequency of Treatment: Once every 14 days for 17 treatments.

Duration of Study: 203 days

Parameters Measured: Males received at least seven treatments prior to the first mating. Clinical observations were made before and at multiple times after treatment. General health of each dog was evaluated twice daily throughout the study. Blood, urine, and feces were collected and evaluated for clinical pathology at the beginning of the study, approximately every 28 days and at the end of the study. Semen samples were collected and evaluated for volume, color, pH, sperm count, motility, cytology and morphology weekly prior to initial treatment and approximately every 28 days during the study and at the end of the study. Each male dog was mated to 2 female dogs. Within 24 hours after parturition, all puppies were evaluated to determine litter size and the presence of congenital abnormalities. The number of successful matings, number of puppies/litter, and number of viable puppies/litter were recorded.

Results: There were no adverse effects attributable to administration of selamectin in any of the clinical pathology variables or in any of the reproductive parameters measured in the study. Hair clumping, powdery residue, and hair discoloration were commonly observed at the treatment site for all groups receiving the test article.

Conclusions: Topical administration of selamectin once every 14 days for 17 treatments at three times the recommended minimum dosage of 6 mg/kg had no effect on the health or reproductive status of breeding male dogs.

7. Reproductive Safety Study in Female Dogs: 1466N-60-96-195

Purpose: To evaluate the safety of selamectin in breeding female dogs.

Investigator: Juliann Ehrhart

Study Location: White Eagle Toxicology Laboratories
Doylestown, Pennsylvania

Animals: Forty-four mature female beagle dogs, 22 per treatment group. All dogs were documented dams of at least two recent litters of at least four puppies per litter with no congenital abnormalities in any puppies. Twenty mature male beagles were used for breeding and did not receive any treatment.

Dosage Groups: T1: Saline, treatment initiated day 1 post-mating
T2: Saline, treatment initiated day 15 post-mating
T3: Selamectin (≥18 mg/kg), 3x, treatment initiated day 1 post-mating
T4: Selamectin (≥18 mg/kg), 3x, treatment initiated day 15 post-mating
T5: Saline, not mated
T6: Selamectin (≥18 mg/kg), not mated

Route of Administration: Topical

Frequency of Treatment: Once every 28 days

Duration of Study: 226 days

Parameters Measured: Females received at least two treatments prior to mating and continued to receive treatment until the puppies were 42 days old. Clinical observations were made before and at multiple times after treatment. General health of each dog was evaluated at multiple times daily throughout the study. Blood, urine, and feces were collected and evaluated for clinical pathology approximately every 28 days and at the end of the study. Females were mated and conception rate, whelping index, and weaning index were calculated for each litter. All puppies were evaluated for the presence of congenital abnormalities. General health of each puppy was evaluated twice daily until weaning.

Results: There were no adverse effects attributable to administration of selamectin in any of the clinical pathology variables or in any of the reproductive parameters measured in the study. Hair clumping, powdery residue, and hair discoloration were commonly observed in all dogs treated with the test article.

Conclusions: Topical administration of selamectin once every 28 days at three times the recommended minimum dosage of 6 mg/kg had no effect on the health or reproductive status of breeding female dogs.

VIII. HUMAN SAFETY

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA. This drug is to be labeled for use in dogs and cats which are non-food animals.

Human Warnings are provided on the product label as follows: "May be irritating to skin and eyes. Wash hands after use and wash off any product in contact with the skin immediately with soap and water. If contact with eyes occurs, then flush eyes copiously with water. In case of ingestion by a human, contact a physician immediately. The material safety data sheet (MSDS) provides more

detailed occupational safety information. For a copy of the MSDS or to report adverse reactions attributable to exposure to this product, call 1-800-366-5288.

Flammable - Keep away from heat, sparks, open flames or other sources of ignition."

IX. AGENCY CONCLUSIONS

The data in support of this NADA comply with the requirements of Section 512 of the Act and Section 514 of the implementing regulations. The data demonstrate that Revolution (selamectin) topical for dogs and cats, when used under labeled conditions of use, is safe and effective.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise and proper diagnosis are required to determine the existence of heartworm infections and sarcoptic mange infestations and to monitor the safe use of the product.

Under section 512(c)(2)(F)(i) of the FFDCA, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of approval because no active ingredient (including any ester or salt of the active ingredient) has been approved in any other application.

Pfizer, Inc. patent pending in the U.S.

X. Labeling (Attached)

A. Package Insert
B. Tube Label
C. Blister Label
D. Carton Label
E. Shipping Case Label
F. Calendar Stickers

cc: HFV-199, NADA Orig. 141-152
HFV-2
HFV-12 (FOI Staff)
HFV-102 (GADQC Reserve Copy)
HFV-102 Green Book (Nturner)
HFA-305 (Dockets Management Branch)
HFR-NE250, NEW-DO

ec: CVM Records\ONADE\\N141-152\A0000foi.sum

Package Insert

NADA 141-152, Approved by FDA

REVOLUTION™ (Selamectin)
Topical Parasiticide For Dogs and Cats

CAUTION:
US Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION:
Revolution (selamectin) Topical Parasiticide is available as a colorless to yellow, ready to use solution in single dose tubes for topical (dermal) treatment of dogs and cats six weeks of age and older. The content of each tube is formulated to provide a minimum of 2.7 mg/lb (6 mg/kg) of body weight of selamectin. The chemical composition of selamectin is (5Z,25S)-25-cyclohexyl-4'-O-de(2,6-dideoxy-3-O-methyl-α-L-arabino-hexopyranosyl)-5-demethoxy-25-de(1-methylpropyl)-22,23-dihydro-5-hydroxyiminoavermectin A_{1a}.

INDICATIONS:
Revolution kills adult fleas and prevents flea eggs from hatching for one month and is indicated for the prevention and control of flea infestations (*Ctenocephalides felis*), prevention of heartworm disease caused by *Dirofilaria immitis*, and the treatment and control of ear mite (*Otodectes cynotis*) infestations in dogs and cats. Revolution also is indicated for the treatment and control of sarcoptic mange (*Sarcoptes scabiei*) in dogs, and the treatment of intestinal hookworm (*Ancylostoma tubaeforme*) and roundworm (*Toxocara cati*) infections in cats. Revolution is recommended for use in dogs and cats six weeks of age and older.

WARNINGS:
Not for human use. Keep out of the reach of children.
May be irritating to skin and eyes. Wash hands after use and wash off any product in contact with the skin immediately with soap and water. If contact with eyes occurs, then flush eyes copiously with water. In case of ingestion by a human, contact a physician immediately. The material safety data sheet (MSDS) provides more detailed occupational safety information. For a copy of the MSDS or to report adverse reactions attributable to exposure to this product, call 1-800-366-5288.

Flammable - Keep away from heat, sparks, open flames or other sources of ignition.

PRECAUTIONS:
Use with caution in sick, debilitated or underweight animals (see SAFETY).
Prior to administration of Revolution, dogs should be tested for existing heartworm infections. At the discretion of the veterinarian, infected dogs should be treated to remove adult heartworms. Revolution is not effective against adult *D. immitis* and, while the number of circulating microfilariae may decrease following treatment, Revolution is not effective for microfilariae clearance.

Hypersensitivity reactions have not been observed in dogs with patent heartworm infections administered three times the recommended dose of Revolution. Higher doses were not tested.

ADVERSE REACTIONS:
Following treatment with Revolution transient localized alopecia with or without inflammation at or near the site of application was observed in approximately 1% of 691 treated cats. Other signs observed rarely (≤0.5% of 1743 treated cats and dogs) included vomiting, loose stool or diarrhea with or without blood, anorexia, lethargy, salivation, tachypnea, and muscle tremors.

DOSAGE:
The recommended minimum dose is 2.7 mg selamectin per pound (6 mg/kg) of body weight.
Administer the entire contents of a single dose tube of Revolution topically in accordance with the following tables. (see ADMINISTRATION for the recommended treatment intervals).

Cats (lb)	Package color	mg per tube	Potency (mg/mL)	Administered volume (mL)
Up to 5	Mauve	15 mg	60	0.25
5.1–15	Blue	45 mg	60	0.75

For cats over 15 lbs use the appropriate combination of tubes.

Dogs (lb)	Package color	mg per tube	Potency (mg/mL)	Administered volume (mL)
Up to 5	Mauve	15 mg	60	0.25
5.1–10	Purple	30 mg	120	0.25
10.1–20	Brown	60 mg	120	0.5
20.1–40	Red	120 mg	120	1.0
40.1–85	Teal	240 mg	120	2.0

For dogs over 85 lbs use the appropriate combination of tubes.
Recommended for use in animals 6 weeks of age and older.

ADMINISTRATION:
Firmly depress the cap to puncture the seal on the Revolution tube; then remove the cap to administer the product.

Part the hair on the back of the animal at the base of the neck in front of the shoulder blades until the skin is visible. Place the tip of the tube on the skin and squeeze the tube to empty its entire contents directly onto the skin in one spot. Do not massage the product into the skin. Due to alcohol content, do not apply to broken skin. Avoid contact between the product and fingers. Do not apply when the hair coat is wet. Bathing or shampooing the animal 2 or more hours after treatment will not reduce the effectiveness of Revolution. Stiff hair, clumping of hair, hair discoloration, or a slight powdery residue may be observed at the treatment site in some animals. These effects are temporary and do not affect the safety or effectiveness of the product. Discard empty tubes in your ordinary household refuse.

Flea Control in Dogs and Cats
For the prevention and control of flea infestations, Revolution should be administered at monthly intervals throughout the flea season, starting one month before fleas become active. In controlled laboratory studies >98% of fleas were killed within 36 hours. Results of clinical field studies using Revolution monthly demonstrated >90% control of flea infestations within 30 days of the first dose. Dogs and cats treated with Revolution, including those with pre-existing flea allergy dermatitis, showed improvement in clinical signs associated with fleas as a direct result of eliminating the fleas from the animals and their environment.

If the dog or cat is already infested with fleas when the first dose of Revolution is administered, adult fleas on the animal are killed and no viable fleas hatch from eggs after the first administration. However, an environmental infestation of fleas may persist for a short time after beginning treatment with Revolution because of the emergence of adult fleas from pupae.

Heartworm Prevention in Dogs and Cats
For the prevention of heartworm disease, Revolution must be administered on a monthly basis. Revolution may be administered year-round or at least within one month after the animal's first exposure to mosquitoes and monthly thereafter until the end of the mosquito season. The final dose must be given within one month after the last exposure to mosquitoes. If a dose is missed and a monthly interval between dosing is exceeded then immediate administration of Revolution and resumption of monthly dosing will minimize the opportunity for the development of adult heartworms. When replacing another heartworm preventive product in a heartworm disease prevention program, the first dose of Revolution must be given within a month of the last dose of the former medication.

At the discretion of the veterinarian, cats ≥6 months of age may be tested to determine the presence of existing heartworm infections before beginning treatment with Revolution. Cats already infected with adult heartworms can safely be given Revolution monthly to prevent further infections.

Ear Mite Treatment in Dogs and Cats
For the treatment of ear mite (*O. cynotis*) infestations in dogs and cats, Revolution should be administered once as a single topical dose. A second monthly dose may be required in some dogs. Monthly use of Revolution will control any subsequent ear mite infestations. In the clinical field trials ears were not cleaned, and many animals still had debris in their ears after the second dose. Cleansing of the infested ears is recommended to remove the debris.

Sarcoptic Mange Treatment in Dogs
For the treatment of sarcoptic mange (*S. scabiei*) in dogs, Revolution should be administered once as a single topical dose. A second monthly dose may be required in some dogs. Monthly use of Revolution will control any subsequent sarcoptic mange mite infestations. Because of the difficulty in finding sarcoptic mange mites on skin scrapings, effectiveness assessments also were based on resolution of clinical signs. Resolution of the pruritus associated with the mite infestations was observed in approximately 50% of the dogs 30 days after the first treatment and in approximately 90% of the dogs 30 days after the second monthly treatment.

Nematode Treatment in Cats
For the treatment of intestinal hookworm (*A. tubaeforme*) and roundworm (*T. cati*) infections, Revolution should be applied once as a single topical dose.

SAFETY:
Revolution has been tested safe in over 100 different pure and mixed breeds of healthy dogs and over 15 different pure and mixed breeds of healthy cats, including pregnant and lactating females, breeding males and females, puppies and kittens six weeks of age and older, and avermectin-sensitive collies. However, a kitten, estimated to be 5-6 weeks old (0.3 kg), died 8½ hours after receiving a single treatment of Revolution at the recommended dosage. The kitten displayed clinical signs which included muscle spasms, salivation and neurological signs. The kitten was a stray with an unknown history and was malnourished and underweight (see PRECAUTIONS).

DOGS: In safety studies Revolution was administered at 1, 3, 5, and 10 times the recommended dose to 6 week old puppies, and no adverse reactions were observed. The safety of Revolution administered orally also was tested in case of accidental oral ingestion. Oral administration of Revolution at the recommended topical dose in 5 to 8 month old beagles did not cause any adverse reactions. In a pre-clinical study selamectin was dosed orally to ivermectin-sensitive collies. Oral administration of 2.5, 10, and 15 mg/kg in this dose escalating study did not cause any adverse reactions; however, eight hours after receiving 5 mg/kg orally, one avermectin-sensitive collie became ataxic for several hours, but did not show any other adverse reactions after receiving subsequent doses of 10 and 15 mg/kg orally. In a topical safety study conducted with avermectin-sensitive collies at 1, 3 and 5 times the recommended dose of Revolution, salivation was observed in all treatment groups, including the vehicle control. Revolution also was administered at 3 times the recommended dose to heartworm infected dogs, and no adverse effects were observed.

CATS: In safety studies, Revolution was applied at 1, 3, 5, and 10 times the recommended dose to six week old kittens. No adverse reactions were observed. The safety of Revolution administered orally also was tested in case of accidental oral ingestion. Oral administration of the recommended topical dose of Revolution to cats caused salivation and intermittent vomiting. Revolution also was applied at 4 times the recommended dose to patent heartworm infected cats, and no adverse reactions were observed.

In well-controlled clinical studies, Revolution was used safely in animals receiving other frequently used veterinary products such as vaccines, anthelmintics, antiparasitics, antibiotics, steroids, collars, shampoos and dips.

STORAGE CONDITIONS: Store below 30°C (86°F).

HOW SUPPLIED: Available in six separate dose strengths for dogs and cats of different weights (see Dosage). Each strength comes in a carton containing either 3 single dose tubes (puppy/kitten package) or 6 single dose tubes (all other sizes).

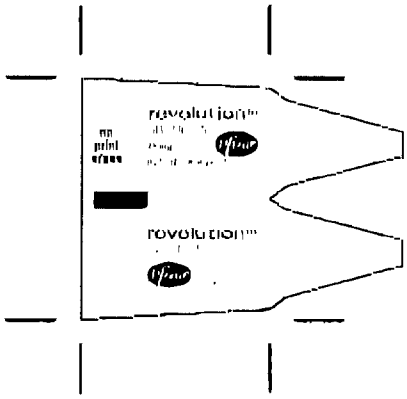
Distributed by:
Pfizer Animal Health
Exton, PA 19341, USA
Div. of Pfizer Inc, NY, NY 10017

www.revolutionpets.com

995

69-9660-00-0

Tube Label



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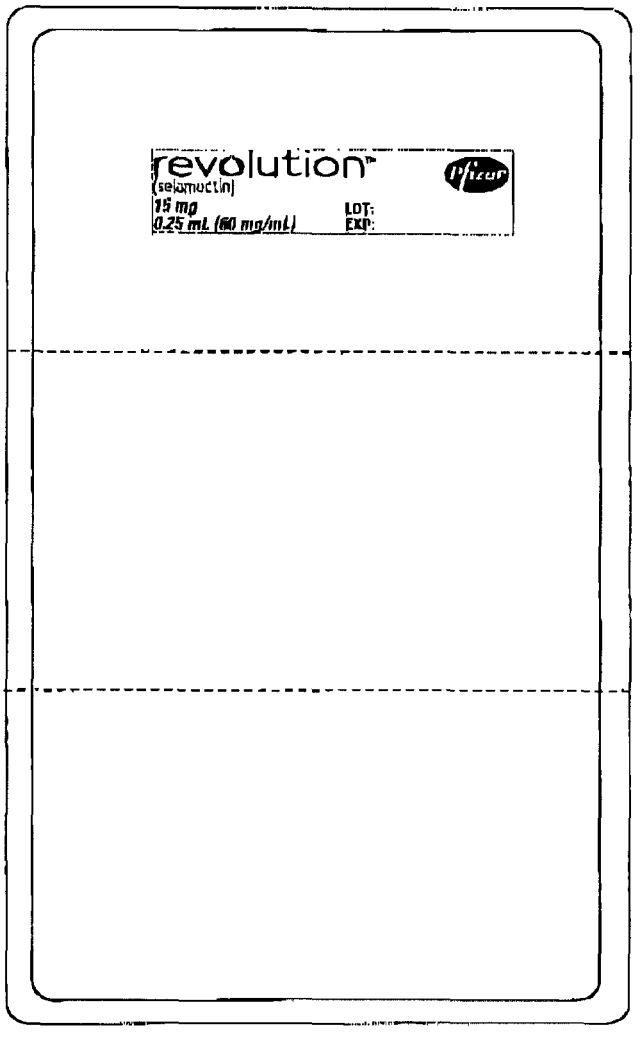
(printable area)

PMS 088 Black

49-9488--0 12/11/98

Vendor Artwork Number — 01-9488-00-0

Blister Label



1.875" (W) x .459" (H)
(printable area)

Black

01-9660-00-0 Draft #1 5/07/99

Vendor Artwork Number — 01-9660-00-0

Carton Label (Front)

Convenient once-a-month topical parasiticide for puppies & kittens ≤ 5 lbs in weight and at least 6 weeks of age

Three single-dose tubes each containing 0.25 mL (6 mg of selamectin) for puppies & kittens ≤ 5 lbs in weight and at least 6 weeks of age

revolution™ (selamectin)

revolution™ (selamectin)

Pfizer

Caution: U.S. Federal law restricts this drug to use by or on the order of a licensed veterinarian.
For use in animals only. Keep out of reach of children.
NADA 141-152, Approved by FDA

English U.S. – Dogs & Cats ≤ 5 lbs
TCG Reader #5 5/10/99

THE COLEMAN GROUP

Client	Pfizer	File Name	5 lbs Puppy & Kitten/r5
Product Name	Revolution	Applications	Adobe Illustrator 7.0
Project No	5587	Fonts	CG Bernhard/Helvetica/Times
Item Shown	Dogs & Cats ≤ 5 lbs		
Die No	2858lr3	Date	5/10/99
Revised By	Chris Lukes	Contact	Delza Lazamann

The Coleman Group, LLC 300 Park Avenue South New York NY 10010
Tel 212 375 0550 Fax 212 982 1864 www.colemangroup.com

Carton Label (Inside)

revolution™ (selamectin)

Dose and Administration: Revolution is recommended for use in puppies/kittens six weeks of age and older. Apply to the skin at the recommended minimum dose of 2.7 mg of selamectin per lb (6 mg/kg) of body weight once a month.

To facilitate application of Revolution, follow these basic steps. Revolution should be applied when the pet's haircoat is dry. However, bathing or immersing your pet in water 2 hours after application will not reduce the effectiveness of this treatment.

1. Remove the Revolution tube from its protective package.

2. Holding the tube upright, firmly depress the cap to puncture the applicator seal, then remove the cap.

3. Part the hair on the back of the animal at the base of the neck, in front of the shoulder blades, until the skin is visible.

4. Apply the tip of the Revolution tube directly to the skin without massaging. Squeeze the tube firmly to empty the contents in one spot. Avoid contact between Revolution and your fingers.

Discard empty tubes in your ordinary household refuse.

Q. Can I give my pet a bath after administration?
A. Yes, studies show that effectiveness is not reduced by bathing or immersing your pet in water two hours after application.

Q. How safe is Revolution for my pet?
A. Revolution has demonstrated a wide margin of safety in healthy animals 6 weeks of age and older. In field studies, vomiting, diarrhea and temporary, localized hair loss at the application site were observed in <1% of the treated animals.

Q. When can I play with my pet following treatment with Revolution?
A. You may hold or play with your pet any time after the area on which Revolution was applied is dry. You should avoid contact with application site when wet.

Q. Are there any precautions I should consider when using Revolution?
A. As with any prescription medication, you should always follow label directions. For topical use only. Use with caution in sick, debilitated or underweight animals.

Q. How should I store Revolution?
A. Revolution should be stored in its original carton at or below room temperature of 30°C or 86°F. After application, empty tubes can be placed in your normal household refuse for disposal.

See package insert for full product information.

PANTONE 110 C | PANTONE 688 C | Process BLACK C

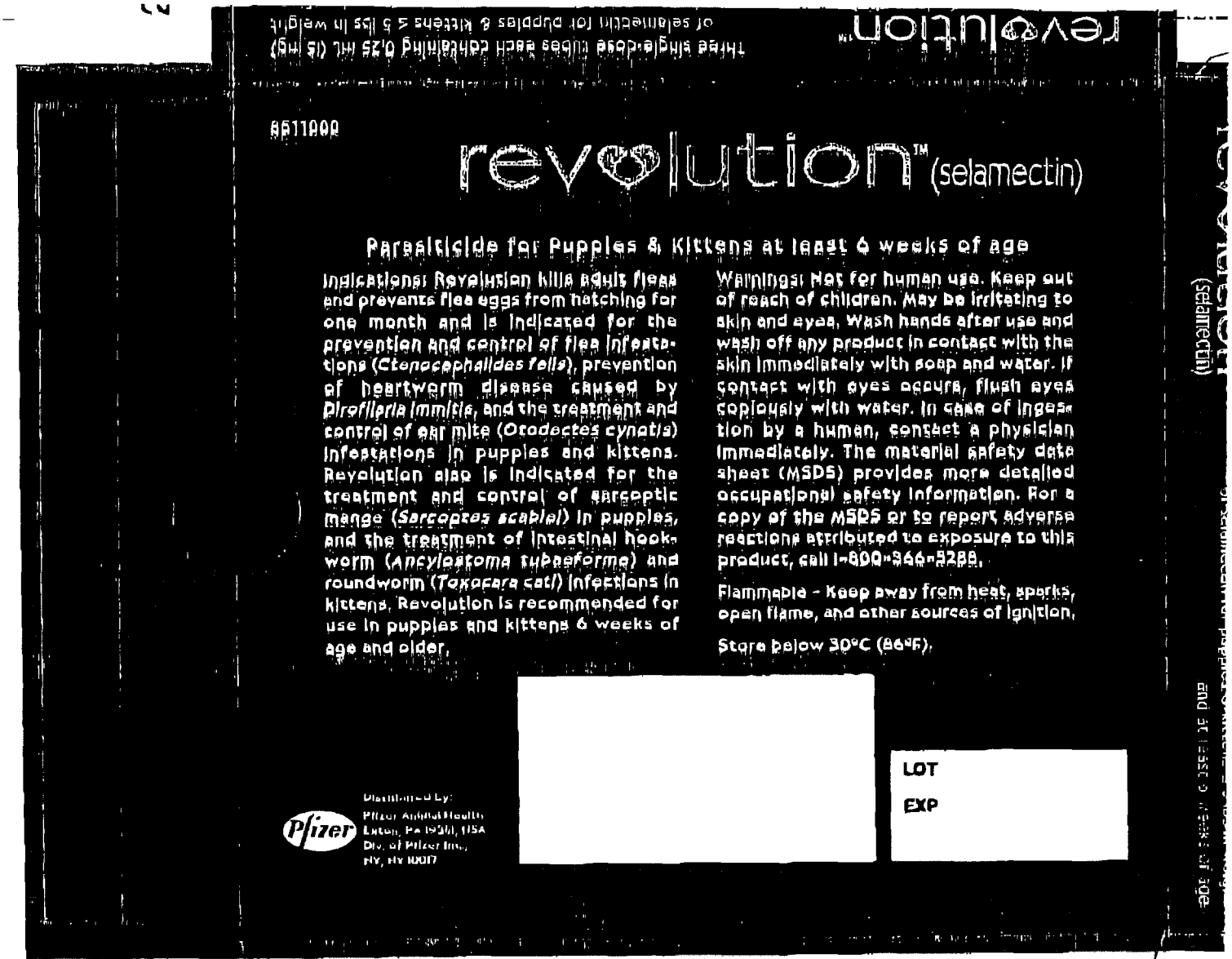
English U.S. – Dogs & Cats ≤ 5 lbs Inside

TCG Reader #4 4/27/99

THE COLEMAN GROUP

Client	Pfizer	File Name	5 lbs Puppy & Kitten Inside/r4
Product Name	Revolution	Application	Adobe Illustrator 7.0
Project No.	5587	Fonts	OG Bernhard/Helvetica/Times
Item Shown	Dogs & Cats ≤ 5 lbs		
Die No.	28588d3	Date	4/27/99
Revised By	Chris Lukas	Created	Debra Lassonara

The Coleman Group, L.L.C. 300 Park Avenue South New York NY 10010
Tel 212 375 0550 Fax 212 982 1964 www.colemangroup.com



Carton Label (Back)

PANTONE 110 C	PANTONE 688 C	Process BLACK C	Process CYAN C	Process MAGENTA	Process YELLOW

10 x 851100

revolution™
(selamectin)

Store Below 30°C (86°F)

Warning: Flammable! Keep away from heat, sparks, open flame, and other sources of ignition.

0.25 mL (60 mg/mL)

Distributed by:
Pfizer Animal Health
Exton, PA 19341, USA
Div. of Pfizer Inc
NY, NY 10017

10 x 851100

revolution™
(selamectin)

Store Below 30°C (86°F)

Warning: Flammable! Keep away from heat, sparks, open flame, and other sources of ignition.

0.25 mL (60 mg/mL)

LOT
EXP

995
04-9560-00-0
Made in USA

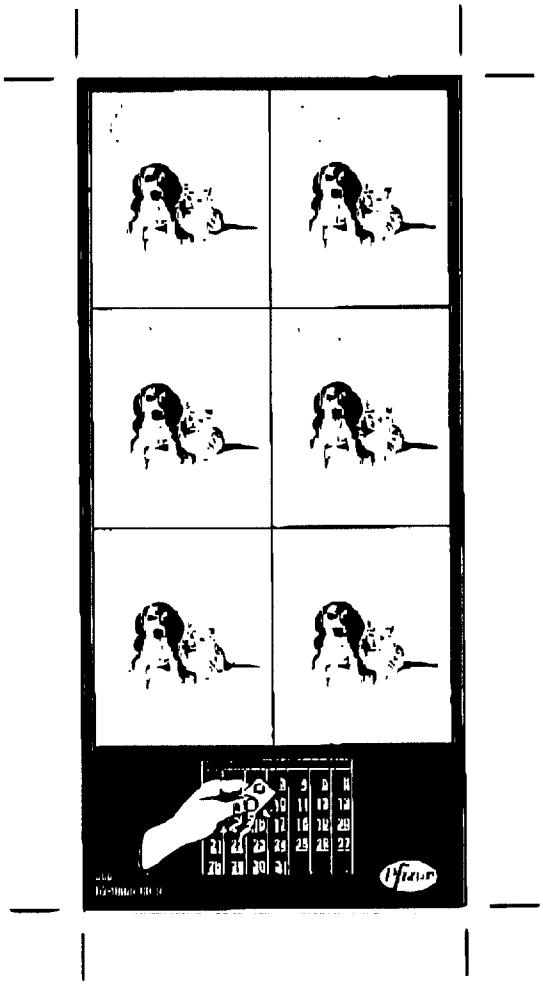
10" (W) x 4" (H)

Code 128: 049660000

Black

04-9660-00-0 Draft #1 5/07/99

Shipping Case Label



2" (W) x 4 ½" (H)

4-Color Process | PMS 110 | PMS 689

02-9666-00-0 Draft #1 5/6/99